BRAIN IMAGING IN SCHIZOPHRENIA

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I hereby declare that:

(a) this thesis has been composed by myself

and that:

(b) the work it describes was largely conducted by myself, in collaboration with a number of research workers from the MRC Brain Metabolism Unit and the Edinburgh University Department of Psychiatry at the Royal Edinburgh Hospital

and that:

(c) those parts of the work which were not completed entirely by myself are clearly identified in the acknowledgements' sections at the end of each relevant chapter

Signed..... .....

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THE UNIVERSITY OF EDINBURGH

ABSTRACT OF THESIS

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Patients with schizophrenia, as a group, have several abnormalities of brain structure and function as compared with normal controls. In particular, they have enlarged ventricles and a loss of brain substance ("atrophy") on Computerised Tomography; and a reduction in the volumes of the whole brain and mesial temporal lobe structures on Magnetic Resonance Imaging (MRI). Functional brain scanning studies, such as Single Photon Emission Tomography (SPET) and Positron Emission Tomography, have generally revealed reduced regional cerebral blood flow (rCBF) or neuronal metabolism in the frontal lobes ("hypofrontality"). Chapter 1 reviews this literature, including a systematic and quantitative review of the volumetric MRI studies to date, and examines the links between such biological findings and the clinical features of the illness.

Chapter 2 describes an original piece of research designed to examine the biological associations of treatment response in schizophrenia with MRI, SPET and detailed neuropsychological testing. Forty patients were selected as treatment responsive or resistant using standardised criteria. A quantitative analysis of particular regional volumes on MRI revealed that the treatment resistant group had a consistent, but not statistically significant, tendency to smaller cerebral structures. Qualitative ratings showed a tendency to greater atrophy in the treatment resistant patients. The SPET scans did not detect any significant between group differences. Treatment resistant cases demonstrated significantly worse performance on several cognitive measures, and the difference on a test of episodic memory remained after controlling for global intellectual deficits, years of education or current medication levels.

The forty SPET scans were subsequently used in a comparison of rCBF in medicated and unmedicated schizophrenia, other psychotic patients and normal controls. The schizophrenic patients showed the predicted hypofrontality, but this was limited to the anterior cingulate and medial pre-frontal cortex (Ebmeier *et al.*, 1995). Given some evidence, from post-mortem studies, of a preferential loss of gaba-ergic neurones in the anterior cingulate in schizophrenia, with a compensatory upregulation of non-specific GABA-A receptor binding, a study of GABA receptor binding on SPET was conducted using the benzodiazepine ligand Iomazenil. As described in Chapter 3, the expectation was that Iomazenil binding would be increased in frontal regions, but this was not confirmed in a comparison of ten schizophrenics and ten normal controls; and an apparent reduction of subcortical receptor binding was attributed to methodological problems.

Finally, Chapter 4 describes the likely technical and experimental developments in brain imaging studies of schizophrenia in the foreseeable future. Some recommendations are made, based on these advances and the studies described in the thesis, that would help to exploit the full potential of neuroimaging to improve understanding of the pathophysiology of schizophrenia.

TABLE OF CONTENTS

	Page No.
CHAPTER 1 - LITERATURE REVIEW	1
1. INTRODUCTION	2
1.1 COMPUTERISED TOMOGRAPHY (CT)	3
1.1.2 POTENTIAL ARTEFACTS ON CT	4
1.1.3 CT FINDINGS IN SCHIZOPHRENIA	5
1.1.4 CONCLUSIONS FROM CT STUDIES IN SCHIZOPHRENIA	11
1.2 MAGNETIC RESONANCE IMAGING (MRI)	12
1.2.2 METHODOLOGICAL PROBLEMS AND ARTEFACTS IN MRI	15
1.2.3 MRI STUDIES IN PATIENTS WITH SCHIZOPHRENIA	17
1.2.4 CONCLUSIONS FROM MRI STUDIES IN SCHIZOPHRENIA	53
1.3 FUNCTIONAL BRAIN IMAGING	56
1.3.1 SINGLE PHOTON EMISSION TOMOGRAPHY (SPET)	57
1.3.2 SPET IMAGE ANALYSIS AND POTENTIAL ARTEFACTS	60
1.3.3 SPET STUDIES IN NORMAL SUBJECTS	62
1.3.4 SPET STUDIES IN SCHIZOPHRENIA	64
1.3.5 CONCLUSIONS FROM SPET STUDIES IN SCHIZOPHRENIA	70
1.4 POSITRON EMISSION TOMOGRAPHY (PET)	71
1.4.2 PET METHODOLOGICAL PROBLEMS AND ARTEFACTS	74
1.4.3 PET STUDIES IN NORMAL SUBJECTS	76
1.4.4 PET STUDIES IN SCHIZOPHRENIA	77
1.4.5 ARE THE PET FINDINGS SPECIFIC TO SCHIZOPHRENIA?	85
1.4.6 CONCLUSIONS FROM PET STUDIES IN SCHIZOPHRENIA	86
CHAPTER 2 - STUDY I - MAGNETIC RESONANCE IMAGING, SINGLE PHOTON EMISSION TOMOGRAPHY AND NEUROPSYCHOLOGICAL ASSESSMENT IN TREATMENT RESPONSIVE AND TREATMENT RESISTANT SCHIZOPHRENIA	87
2.1 INTRODUCTION	88
2.2 METHODS	90
2.3 RESULTS	99
2.4 DISCUSSION	117
2.5 CONCLUSIONS	125
2.6 ACKNOWLEDGEMENTS	126
CHAPTER 3 - STUDY II - I^{123}-IOMAZENIL BINDING ON SINGLE PHOTON EMISSION TOMOGRAPHY IN SCHIZOPHRENIA	127
3.1 INTRODUCTION	128
3.2 METHODS	132
3.3 RESULTS	136
3.4 DISCUSSION	148
3.5 CONCLUSIONS	155
3.6 ACKNOWLEDGEMENTS	156
CHAPTER 4 - THE FUTURE OF BRAIN IMAGING IN SCHIZOPHRENIA	157
4.1 INTRODUCTION	158
4.2 TECHNICAL DEVELOPMENTS	159
4.3 THEORETICAL DEVELOPMENTS	163
4.4 CONCLUSIONS	178
REFERENCES	180

CHAPTER 1

LITERATURE REVIEW

1. INTRODUCTION

There is a consensus nowadays that the syndrome of schizophrenia is largely a manifestation of one or more disturbances in brain structure and function. This idea has received most support over the past twenty years, mainly from a variety of techniques used to image the brain, but was proposed a century ago. Emil Kraepelin was not only the first to suggest a distinction between the two main types of 'functional' psychosis, but also among the first to suggest that 'dementia praecox' was associated with some neuropathological disturbance (Kraepelin, 1919). Shortly afterwards, his subjective and qualitative observations were supported by investigations with pneumoencephalography, which was the first attempt to image the brain *in vivo*. After lumbar puncture, cerebro-spinal fluid (CSF) was withdrawn and replaced with air to outline the cerebral ventricles and cortical surface on x-ray reoentography (Dandy, 1918). The technique was first applied to psychiatric patients by Jacobi & Winkler (1927), who described an apparent loss of brain tissue in patients with schizophrenia. As a result of the risks and discomfort involved, pneumoencephalography was not extensively used to study clinical populations, but patients with schizophrenia appeared to exhibit enlarged lateral and third ventricles, as well as widened cortical sulci (Haug, 1982; Weinberger & Wyatt, 1982).

These findings were largely ignored, probably because of a psychoanalytical hegemony within the psychiatric profession, but it has not been possible to disregard subsequent findings with an increasing array of sophisticated and complimentary neuro-imaging methods. This introductory chapter will briefly describe these methods and their limitations, summarise the main findings obtained with them, and identify some important questions for future study. Structural techniques - computerised tomography and, in particular, magnetic resonance imaging - will be reviewed first; followed by an account of the main functional imaging methods of single photon emission (computed) tomography and positron emission tomography. Relevant results from post-mortem studies will be mentioned where pertinent to this and subsequent chapters.

1.1 COMPUTERISED TOMOGRAPHY (CT)

The last study to use pneumoencephalography (Haug, 1982) was actually published several years after the first account of CT in schizophrenia, which, as a relatively safe and non-invasive method of imaging the brain, presented researchers with many new experimental opportunities. CT images are obtained from the reconstruction of X-ray radiation transmission from multiple projections around the object of interest; the accurate measurement of the X-ray attenuation depending on the sensitivity of photomultiplier tubes and a sodium iodide detector. The independent realisation of this possibility earned Cormack and Hounsfield a joint award of the 1979 Nobel prize for medicine/physiology. The clinical use of CT began in 1971 and findings were first published in 1973 (Hounsfield, 1973). The first use of the technique in patients with schizophrenia quickly followed, in which the outline of the ventricles and the brain were traced by planimetry and the Ventricle:Brain Ratio (VBR) was calculated (Johnstone *et al.*, 1976). The finding of relatively enlarged ventricles in chronic schizophrenics as opposed to controls of similar age was soon replicated (Weinberger *et al.*, 1979), and has now been so in over 100 controlled CT studies (Lewis, 1990). Despite the inevitable scanning artefacts (especially "beam hardening" and partial volume effects), limitations of the technique (to area measures in one plane) and variations in study methodology (particularly in ascertaining measurements and the composition of patient and control groups) a remarkable degree of consensus has emerged - that patients with schizophrenia have, as a group, enlarged lateral and third ventricles and increased cerebral 'atrophy' (Lewis, 1990). Thus, early suggestions from pneumoencephalography have been confirmed and certain other differences between schizophrenic and control populations were also suggested. These findings and their clinical associations will be briefly reviewed, after a consideration of some of the more pertinent artefacts that can be troublesome in the interpretation of CT scan images.

1.1.2 POTENTIAL ARTEFACTS ON CT

The main artefacts of CT scanning, given that the x-ray source and detection is correctly aligned and calibrated, arise from the absorption of lower energy x-ray photons as they pass through tissue so that the beam becomes composed of higher energy rays and attenuation values are generally lowered - particularly around bony structures - so that peripheral structures are assigned relatively less dense CT values ("beam hardening"). Scattering of x-rays around dense objects such as bone can produce streak effects, as does patient motion. Partial volume effects are common to all imaging techniques, arising from the fitting of linear geometry onto non-linear anatomical structures, and leading to a loss of spatial and tissue resolution (of at least 1-2 mm), although the exact cause and nature of the effect differs between different imaging methods. In CT scanning, boundary tissue will be assigned the CT number of the average of the adjacent tissues, which may be invalid and is particularly problematic if comparatively thick slices are used. For all the above reasons comparing absolute CT numbers, as measures of "cerebral density", can be highly misleading (Jacobson *et al.*, 1985; Coffman, 1989). Researchers have nonetheless tried to do this as a way of localising the neuroanatomical deficit(s) in schizophrenia, and many have reported variable abnormalities of 'hypodensity' or in left-right asymmetry. Perhaps the most interesting finding in this area is from the study of monozygotic discordant twins (Reveley *et al.*, 1987), where the schizophrenic co-twins were found to have consistently less dense left cerebral hemispheres. However, such results have not been consistently replicated - probably because of the inherent unreliability of these measures, the fact that they could simply reflect a generalised loss of cerebral substance, and because of the limited spatial resolution with CT. For these reasons, most researchers have concluded that CT cannot provide sufficiently detailed information on regional abnormalities in schizophrenia (e.g. Pearlson *et al.*, 1989; Daniel *et al.*, 1991a). Attention has been more usefully devoted towards identifying the clinical associations and course of consistently reported CT abnormalities, such as ventriculomegaly and cerebral atrophy.

1.1.3 CT FINDINGS IN SCHIZOPHRENIA

1.1.3.1 Lateral Ventricle Enlargement

Although the vast majority of studies have demonstrated relative ventriculomegaly in groups of schizophrenics (Coffman, 1989; Lewis, 1990), only about a third of individual patients exhibit this to a degree well above (i.e. two standard deviations) a control mean. Moreover, such case-control differences are more marked when medical controls, with proven normal scans, are used (Smith & Iacono, 1986; Smith *et al.*, 1988); suggesting the possibility of Type I error. The findings that malnutrition (Heinz *et al.*, 1977; Handler *et al.*, 1981), hypercortisolaemia (Heinz *et al.*, 1977; Bentson *et al.*, 1978) and alcoholism (Carlen *et al.*, 1978) can cause (reversible) ventriculomegaly suggest that psychiatric treatment, institutionalisation or superimposed medical illness could play a part in the process(es) determining ventricular enlargement. However, repeated findings that treatment exposure and length of hospitalisation do not correlate strongly with the VBR supports the validity of venticulomegaly in schizophrenia as compared the comparisons with normal controls (e.g. Johnstone *et al.*, 1976; Weinberger *et al.*, 1979; Golden *et al.*, 1980; Nasrallah *et al.*, 1983a; Luchins *et al.*, 1984; Williams *et al.*, 1985; Owens *et al.*, 1985; Pfefferbaum *et al.*, 1988; Johnstone *et al.*, 1989a; Coffman, 1989; Lewis, 1990). Illness duration, however, has been associated with ventricular enlargement in quantitative reviews of the literature (Raz & Raz, 1990; van Horn & McManus, 1992), suggesting that there may be a progressive component or that ventriculomegaly may be a marker for poor prognosis.

Stronger evidence that ventriculomegaly is not simply explained by clinical confounders comes from repeated findings that ventricular enlargement is present at onset in first episode cases (Weinberger *et al.*, 1982; Schulz *et al.*, 1983a; Turner *et al.*, 1986). Furthermore, most studies suggest that it does not appear to progress with time beyond what would be expected with age (Nasrallah *et al.*, 1986a; Illowsky *et al.*, 1988; Vita *et al.*, 1988; Jaskiw *et al.*, 1994), but some do suggest some progression (Woods *et al.*,

1990) and methodological considerations are important here. Woods *et al.* (1991) have shown that a 1mm variation in slice positioning for estimation of the VBR can alter the value by as much as 10%, making it particularly difficult to reliably measure changes over time. Regression to the mean is another consideration, as illustrated by two studies where patients with the smallest VBR show the greatest apparent progression, while those with the largest ventricles actually show a reduction in size over time (Nasrallah *et al.*, 1986a; Kemali *et al.*, 1989).

The lack of relationship to clinical measures, however, raises the possibility that an increased VBR may only be an epiphenomenon of the pathophysiological process leading to schizophrenia. It is therefore reassuring to note that some consistent associations have been found with performance on cognitive testing and to a lesser extent with outcome or treatment response. Indeed, cognitive impairment was significantly associated with ventriculomegaly in the very first CT study in schizophrenia (Johnstone *et al.*, 1976), which was subsequently confirmed by the same authors in a further study (Johnstone *et al.*, 1978), and has been by almost all the other research groups that have examined the relationship (Donnelly *et al.*, 1980; Golden *et al.*, 1980 & 1982; Kemali *et al.*, 1985; Owens *et al.*, 1985; Johnstone *et al.*, 1989). Some have reported that a certain level of cognitive impairment can predict those schizophrenics with and without enlarged ventricles (Donnelly *et al.*, 1980; Golden *et al.*, 1982), although Owens *et al.* (1985) described a curvilinear (inverted-U) relationship.

Less consistently, clinical associations have also been reported between ventricular enlargement and poor premorbid adjustment (Weinberger *et al.*, 1980; Williams *et al.*, 1985; Pearlson *et al.*, 1985); poor treatment response and/or global outcome (Delisi *et al.*, 1983; Smith *et al.*, 1983 & 1985; Schulz *et al.*, 1983b; Luchins *et al.*, 1984; Williams *et al.*, 1985); and extrapyramidal side effects with neuroleptic treatment (Luchins *et al.*, 1983; Owens *et al.*, 1985; Johnstone *et al.*, 1989). However, it is noticeable that most studies have failed to find significant associations between the VBR and (after Crow,

1980) either more negative or less positive symptomatology (Nasrallah *et al.*, 1983a; Pearlson *et al.*, 1984; Williams *et al.*, 1985; Owens *et al.*, 1985; Pfefferbaum *et al.*, 1988; Johnstone *et al.*, 1989a; Kaiya *et al.*, 1989; McCreadie *et al.*, 1989; Pearlson *et al.*, 1989). Neat clinical associations, into sub-types of schizophrenia, are extremely unlikely given the lack of a bimodal distribution of the VBR (Daniel *et al.*, 1991b).

Following a suggested aetiological distinction between two syndromes in schizophrenia (Crow, 1980), many workers tried to establish that patients with greater ventriculomegaly would be those with a more environmental, and less genetic, type of disorder. However, very few studies have reported a positive correlation between obstetric complications and ventricular size (e.g. Turner *et al.*, 1986; Pearlson *et al.*, 1989), and more have not (Pearlson *et al.*, 1985; Nimgaonkar *et al.*, 1988; Johnstone *et al.*, 1989a; Kaiya *et al.*, 1989). Similarly, very few papers have described a significant inverse correlation between family history and ventricular size (e.g. Turner *et al.*, 1986), most have reported no association (Kemali *et al.*, 1985; Pearlson *et al.*, 1985; Nimgaonkar *et al.*, 1988; Johnstone *et al.*, 1989a; Pearlson *et al.*, 1989; Kaiya *et al.*, 1989), while some even suggest a positive correlation (Nasrallah *et al.*, 1983a; Owens *et al.*, 1985; Cannon *et al.*, 1989). CT studies have therefore not elucidated the reasons for ventriculomegaly in schizophrenia.

1.1.3.2 Third Ventricle Enlargement

Although fewer studies have addressed the size of the third ventricle in schizophrenics subjects and controls, the results are much as those described for the lateral ventricles (Coffman, 1989; Lewis, 1990). Indeed, the relationship may be stronger, as schizophrenics more consistently show relative enlargement of this structure when compared to medical controls (Boronow *et al.*, 1985; Smith *et al.*, 1988). In their meta-analysis, Raz & Raz (1990) concluded that the third ventricle was affected to a greater extent than the lateral ventricle once the differences in measurement method (linear and planimetric respectively) were taken into account. Interestingly, therefore, the duration of illness has more often shown a relationship with third ventricle size than lateral ventricular size (e.g. Rieder *et al.*, 1983; Coffman, 1989) and shows a stronger overall association (Raz & Raz, 1990).

1.1.3.3 Widening of Cortical Sulci

Widened sulci are another manifestation of a lack of brain tissue ('atrophy'). Methodological issues are an even greater consideration here than in research on the ventricular system as beam hardening is more pronounced and reliable measurement is more difficult. Despite the many different techniques used to estimate sulcal width, the majority of case-control studies report enlarged sulci in schizophrenic patients (Coffman, 1989; Lewis, 1990). Such 'atrophy' is noticeable in anything up to 40% of patients depending on definition (Lewis, 1990), although the overall effect size appears to be smaller than for the ventriculomegaly (Raz & Raz, 1990). Clinical correlations are generally weak or non-existent, but have often been found with indices of cognitive dysfunction (Johnstone *et al.*, 1978; Weinberger *et al.*, 1979; Nasrallah *et al.*, 1983b; Pfefferbaum *et al.*, 1988; McCreadie *et al.*, 1989; Raz & Raz, 1990). There are suggestions that sulcal widening is most apparent in the frontal and temporal cortex, and the Sylvian fissure in particular, but regional differences did not reach significance on meta-analysis (Raz & Raz, 1990). Intriguingly, from an aetiological perspective, VBR and atrophy ratings do not usually show a significant correlation (Weinberger *et al.*, 1979; Boronow *et al.*, 1985; McCreadie *et al.*, 1989), and any relationship is at most weak (Nasrallah *et al.*, 1983b; Vita *et al.*, 1988), suggesting that two or more distinct disease processes may be operating in schizophrenia (Cannon *et al.*, 1989).

This highlights a potential problem in most CT studies of the clinical associations of the VBR in schizophrenia. In using a ratio measure of ventriculomegaly corrected for variations in brain size, researchers missed the possibility that ventricular enlargement and atrophy could have differing associations. Unfortunately, the importance of this issue was not recognised until late in the research effort (Pearlson *et al.*, 1989), since when some workers have advocated that the effect of brain size on ventricular area should be controlled for with multivariate statistical techniques (Harvey *et al.*, 1990a&b).

1.1.3.4 Other findings

Several CT studies have suggested that cerebellar atrophy may also be found in groups of schizophrenic patients, with a median estimate of 10% as compared to 1% in controls (Coffman, 1989), but posterior fossa structures are particularly prone to artefact on CT. A number of macroscopic abnormalities (e.g. tumours, cysts, vascular malformations) are also occasionally found in patients with schizophrenia - with a prevalence of approximately 6-9% - but these are generally over-represented among psychiatric populations, appear mainly developmental and rarely change medical management (Owens *et al.*, 1980; Lewis, 1990). Another possible abnormality of interest is an apparent reversal of the normal brain asymmetry, where schizophrenics do not show the usual picture of relatively larger right frontal and left occipital lobes ("brain torque") or a longer length of the right hemisphere; but less than half the studies examining this issue have reported it, and uncorrected tilting of the head in the scanning machine could account for the apparent deficit (Coffman, 1989; Zipursky *et al.*, 1990).

One of the key tests of the significance of such CT abnormalities is whether or not they are found in other psychiatric patients. It is sobering to note that all of the above CT findings reported in schizophrenic populations have also been reported in patients with affective disorders (e.g. Rieder *et al.*, 1983; Pearlson *et al.*, 1984), albeit to a lesser extent (e.g. Pearlson *et al.*, 1989), and that the pattern of their clinical associations is very similar, though less well established due to the smaller number of studies (Coffman, 1989). Of interest, however, is the repeated finding that the VBR in affective disorders is generally larger in those with positive psychotic symptoms (and hypercortisolism) as opposed to the putative association with negative symptoms in schizophrenia (Coffman, 1989; Lewis, 1990). However, this could simply be a marker of severity, where a neurodevelopmental model is pertinent to the affective disorders and schizophrenia; although it should be borne in mind that patients with affective disorders who are scanned are likely to be inpatients and may be less typical than scanned schizophrenic subjects.

1.1.4 CONCLUSIONS FROM CT STUDIES IN SCHIZOPHRENIA

The best available evidence supports the view that patients with schizophrenia have enlarged ventricular structures, perhaps particularly the third ventricle, and to a lesser extent enlarged cortical sulci, in comparison with groups of normal controls. These abnormalities are undoubtedly present at the onset of the illness, the possibility remains of a greater progression than that associated with age alone. This supports the view that brain abnormalities are found in schizophrenia and that they primarily reflect a neurodevelopmental aberration, but a neurodegenerative component cannot be excluded. The lack of consistent clinical associations - other than with cognitive impairment - is disappointing, but this can be partly explained by the relatively small sample size in many of these studies. More importantly, such longstanding abnormalities are likely to be trait rather than state markers, although the failure to find consistent clinical associations of ventriculomegaly could also be attributable to confounding comparisons between ventricular and brain areas. However, the lack of a bimodal distribution of ventricular size argues against any distinctive sub-group of schizophrenic patients with brain abnormalities; rather, they should be seen as risk factors for the development of schizophrenia (and possibly all psychosis) that are neither necessary nor sufficient.

The considerable methodological problems associated with CT - being restricted to the axial plane and linear or area measures rather than volumes, exposing patients to x-rays, and difficulties viewing the posterior fossa or peripheral structures with any reliability - all suggest that this technique is now of little research value in comparison with structural magnetic resonance imaging. MRI not only has technical advantages over CT - of improved resolution, multiplanar three dimensional image acquisition (for volume estimation), enhanced soft tissue contrast, and visualisation of temporal or posterior structures without bone artefact - but it also does not expose patients to the potentially harmful effects of radiation.

1.2 MAGNETIC RESONANCE IMAGING (MRI)

The observation that the structure of a tissue could be inferred from studying the changes when a magnetic field was applied to atomic nuclei was made by both Bloch and Purcell in 1946, for which they shared the Nobel prize for physics in 1952 (Andreasen, 1989). This principle was later developed so that visual images could be developed from the properties of small units of a tissue (Lauterbur, 1973). With technological advances, leading to the availability of the requisite hardware - of both static and gradient magnets, a radio frequency transmitter and receiver, and a computer for data analysis - clinical applications were soon realised (Budinger & Lauterbur, 1984).

The physical basis of the MRI signal is complex and still incompletely understood (Schild, 1990). When a head is placed in the scanner, the protons of water molecules align themselves in the longitudinal orientation of the external magnetic field, either parallel (low energy protons) or anti-parallel (high energy protons), and precess with a rate proportional to the strength of the field. (According to the Larmor equation, the precession frequency is the product of the gyro-magnetic ratio, which is a constant of 42.5 MHz/Tesla for protons, and the field strength in Tesla). The magnetic vectors of proton precession cancel, but there remains some longitudinal magnetisation (LM) of the patients' own magnetic field.

To measure the patients' magnetic field, some transverse magnetisation (TM) is induced by emitting a radio frequency (RF) pulse to synchronise proton precession. The RF pulse must be of the same frequency as the protons so that energy can be exchanged - a phenomenon called resonance. Some protons are lifted to higher energy levels, aligning themselves anti-parallel longitudinally and so reducing LM. The TM changes with the precession frequency of the protons, inducing an electrical current that can be traced anatomically as it is most strong where the magnetic field is strongest and is altered by the proton composition of neighbouring tissues. When the RF pulse is switched off the LM increases and the protons' energy is returned to the surrounding structural lattice (spin-

lattice-relaxation) over time (T1). Simultaneously, the TM is reduced as protons lose their coherence (spin-spin-relaxation) over time (T2). The T1 time constant (300-2000ms) is about 10x longer than the T2 time constant (30-150ms) - in practice, T1 is defined as the time until about 63% of the original LM signal intensity is attained, and T2 as the time until about 37% of the original TM value is returned.

Different tissues have varying relaxation values as they contain differing amounts of hydrogen protons. Tissues with a high water content have both a long T1 and T2 as the transfer of proton energy is difficult at the high frequency precession of water molecules. Fatty tissues have short T1 and T2 values as carbon bonds have frequencies near the Larmor frequency allowing effective energy transfer. The white matter of the brain therefore has a shorter T2 than grey matter. Thus, tissue characteristics and the frequency and timing of RF pulses (in different 'pulse sequences') determine the image derived. Differing pulse sequences have been developed for particular imaging tasks, but the most pertinent to psychiatry are spin-echo and fast imaging sequences.

In a spin echo (SE) sequence, a 180^{o} RF pulse is emitted a certain length of time (tau) after the initial 90^{o} RF pulse (which cancels LM and induces TM), so that protons begin to precess in the opposite direction and faster protons catch up with (previously 'behind') slower protons until they return to phase. A stronger signal will then be generated at the measurement time (2.tau) or time to echo (TE). Further 180^{o} pulses can be repeated after time for complete relaxation (TR). The TE must be long enough to allow tissue contrast, but not so long as to result in low signal to noise - in practice, TE is short if less than 30ms, and long if greater than 80ms. With a SE sequence of long TR and short TE the resultant image is largely free of T1 and T2 effects and determined by proton or spin density (CSF is seen as black, grey matter as white due to higher proton density, and white matter as grey). With a long TE (and long TR) the image is T2 weighted (CSF white, brain as black), while with a short TR (and short TE) the image will

be T1 weighted (CSF black, grey matter grey and white matter white). These sequences generate distinctive images that are useful for identifying brain lesions.

Fast imaging sequences, such Fast Low Angle Shot (FLASH) or Gradient Recalled Acquisition at Steady State (GRASS), shorten the TR and therefore the total imaging time by inducing an additional magnetic field gradient to produce greater field inhomogeneities so that protons dephase faster (according to the T2* curve). Low flip angles, of less than 90^{o} (usually 10^{o}-35^{o}), prevent LM being abolished. If the gradient is switched off and then on again in the opposite direction, a rephasing "gradient echo" is produced. The main problem with fast sequences is that intense flow signals are observed.

The acquisition time is the product of the TR, the number of excitations, and the number of rows in the image matrix (usually 256 rows of 256 picture elements or pixels) and can be shortened by imaging multiple slices simultaneously. Particular orientations are examined by varying the gradient field strength (and therefore precession frequency) produced by the gradient coils; while slice thickness is determined by the slope of the gradient field so that the RF pulse excites only those protons in a location with a particular precession frequency. The anatomical position of the signals emitted is determined by applying gradient fields along the y-axis rows (during RF) and y-axis columns (switched on and off after the RF), so that frequency and phase of particular protons differs slightly according to their location. By Fourier (fast) transformation, the computer assigns location, amplitude, frequency and time to the signals and reconstructs the image. The visual images are produced by automatically assigning shades of white/grey/black to the strength of the signal from relaxing protons detected by the radiofrequency receiver. These signals are subdivided as cubes or voxels (volume elements) of signal corresponding to tissue types, and therefore as shades of grey for integration into picture elements.

1.2.2 METHODOLOGICAL PROBLEMS AND ARTEFACTS IN MRI STUDIES

MRI image acquisition is complex and the final result is dependent on many variables. Small differences in hardware, such as varying field strength, and scanning sequence parameters can have substantial effects on the data collected, making it difficult to reliably conduct multi-centre studies. Visual inspection can identify any lack of standardisation in scan quality, and detect lesions or motion artefact, but the necessary quantitative image analysis is sensitive to a number of potential biases.

Scanner reproducibility should ideally be ensured by establishing the test-retest reliability in the same subjects across time, which has only very recently been reported for the first time (Giedd *et al.*, 1995), but sufficient reliability is likely if scans of a phantom test object are repeated over the duration of a study to allow correction for any signal drift. A standardised head position in the magnetic coil is important to ensure similar signal intensities from the same brain regions in different subjects. Inevitable coil inhomogeneities, which can themselves selectively affect particular regions unless corrected for with a phantom, will otherwise be exaggerated. Head tilt can also cause substantial problems in comparing volumes between cerebral hemispheres either within or between subjects. Tracing regions according to internal anatomical landmarks, if reliable, reduces this problem - as long as all of a structure is examined. If only a set number of slices containing a region are examined, however, tilt correction is essential to avoid omitting the anterior or posterior parts of a structure on one or other side. Partial volume effects are lesser with MRI than CT due to enhanced resolution, but remain a problem where slice thickness exceeds that of the anatomical structure of interest and can also be more pronounced in particular regions if viewed in certain orientations e.g. the ventricular system in transverse rather than coronal section. All of these effects can exceed the inevitable measurement error, particularly in smaller regions (Plante & Turkstra, 1991).

Owing to the time consuming nature of MRI area or volume estimations, even with semi-automated techniques, more than one rater is usually required (and desirable if

reliable volume measurements are to be established) necessitating the calculation of inter-rater reliabilities or mean differences between raters (Bland & Altman, 1986) for the regions examined. Volumetric analyses of anatomical regions are more reliable than linear or area methods, which are inherently unsatisfactory as one or two dimensional measures of complex structures but are also prone to difficulties in ensuring that exactly the same part of the brain is examined in different subjects. Contiguous slices are also preferable to non-contiguous slices for the same reasons. However, even with automatic edge detection programmes and three dimensional images, structure boundaries can be difficult to identify, particularly in complicated structures such as the ventricles.

Inevitably, the earliest MRI studies in schizophrenia reported areas rather than volumes. Moreover, researchers seem to have developed a preoccupation with the size of corpus callosum, perhaps partly because it was so prominent and easily measured on mid-sagital MRI localisers. This early MRI literature will therefore be quickly reviewed, after a brief discussion of studies examining the qualitative appearance of the brain and signal intensity values, before a systematic and detailed consideration of all the published volumetric MRI reports in schizophrenia up to and including June 1996.

1.2.3 MRI STUDIES IN PATIENTS WITH SCHIZOPHRENIA

1.2.3.1 Qualitative MRI appearances

The most obvious advantage of MRI over CT is that of enhanced resolution and greater anatomical detail. As well as improving gross lesion detection, this allows assessment of certain 'qualitative' abnormalities that cannot be easily quantified - such as the degree of cortical atrophy or numbers and types of high intensity signal (HIS) lesions. Indeed, it has been suggested that "visual inspection is as good a measure of cortical atrophy as any, if objectivity is increased by using atrophy rating scales, as no quantitative measure of this is currently in routine use" (Andreasen, 1989). There are, however, few qualitative MRI studies available and they give cortical atrophy rates that vary between 4-40% depending on definition, although these are substantially higher than control rates of 4-7% (Waddington *et al.*, 1990; Harvey *et al.*, 1993; Lewine *et al.*, 1995). The rates of HIS lesions have been reported as 5-22% in patients and 3-19% in controls (Waddington *et al.*, 1990; Harvey *et al.*, 1993; Lewine *et al.*, 1995), with no significant increase in schizophrenia (Johnstone *et al.*, 1986; Harvey *et al.*, 1993) and similar numbers in other psychiatric populations (Lewine *et al.*, 1995), although they may be of a greater extent or volume in patients with schizophrenia than in normal controls (Jernigan *et al.*, 1991).

The most valuable information gained from qualitative MRI scan analysis in schizophrenia research thus far is from studies of the amount and types of gross lesions. Although findings of cerebellar hypoplasia and agenesis of the corpus callosum are rare, with a frequency of only 0-4% (Waddington *et al.*, 1990; Lewine *et al.*, 1995), there have been a number of reports of cavum septum pellucidum in schizophrenia being more common than in psychiatric or normal control subjects (e.g. 25% compared to 10%, Jurjus *et al.*, 1993). Such reports indicate that abnormal midline structures, including the cerebellum (Martin & Albers, 1995), are disturbed as part of the putative neurodevelopmental aberration in schizophrenia, although their precise aetiological significance is uncertain.

1.2.3.2 Quantitative MRI signal parameters

Some early research reported signal intensity values and relaxation times in patients with schizophrenia and controls. Smith *et al.* (1987b) reported increased signal intensities for grey and white matter, especially in left anterior regions, but these results have not been replicated (Johnstone *et al.*, 1986; Kelsoe *et al.*, 1988). Besson *et al.*, (1987) examined spin-lattice (T1) relaxation times in 23 patients and found no differences with controls but did find that increased T1 in frontal, temporal and basal ganglia regions was associated with negative, positive and dyskinetic symptoms respectively. However, these results have also not been directly replicated (Andreasen *et al.*, 1991; Harvey *et al.*, 1991; Buckley *et al.*, 1995), although associations have been reported between prolonged T2 in frontal regions and negative symptoms (Williamson *et al.*, 1991). Quite apart from these inconsistencies, which could be attributed to technical problems such as radio-frequency pulse imperfections, magnetic field inhomogeneities and the need for multiple collections, there is no clear understanding of what changes in T1 or T2 represent pathologically. Relaxation values reflect the concentrations of all the substances in a region of interest and may therefore be affected by a variety of medications (Karlik, 1986). Although specific evidence for similar drug effects are still awaited for psychotropics in the human brain, lithium has been shown to reduce T1 values in bipolar patients (Rangel-Guerra *et al.*, 1982; Rosenthal *et al.*, 1986). Much more information, and a clearer idea of its' meaning, is available from studies of changes in the area or volume of specific brain regions in schizophrenia.

1.2.3.3 Area studies

The first MRI studies in schizophrenia were conducted on small samples and examined areas in machines with very low field strength (0.15-0.5T). Given the unreliability of slice positioning, it is not surprising that the results were inconsistent. Smith *et al.*. (1987b) failed to find significant differences between patients and controls in the VBR, third ventricle and sulcal width, or the corpus callosum to brain ratio. Matthew and colleagues did not identify abnormalities in posterior fossa structures (cerebellar vermis and fourth ventricle), nor cerebral or corpus callosum areas, but did report increased rates of septum pellucidum and corpus callosal lengths (Matthew *et al.*, 1985). Although workers in Iowa (Nasrallah *et al.*, 1986b) found increased callosal area, but not length, their relatively large sample made this an influential paper. Subsequent studies have occasionally reported increased (Uematsu & Kaiya, 1988a) or decreased (Rossi *et al.*, 1989; Woodruff *et al.*, 1993) indices of the corpus callosum, but the most consistent findings have been of no significant case-control differences (e.g. Kelsoe *et al.*, 1988; Raine *et al.*, 1990) and a recent meta-analysis found no significant reduction in callosal area or length relative to brain area (Woodruff *et al.*, 1995). Moreover, methodological problems plague such comparisons (Coppola *et al.*, 1995).

Another report in 1986 from the Iowa group (Andreason *et al.*, 1986) also had a great impact, but mainly because findings of reduced frontal, cerebral and cranial areas in schizophrenia were later attributed to educational and economic advantages in the original hospital staff controls and thereby demonstrated the importance of matching for such variables (Andreasen *et al.*, 1990). This reinforced the findings of DeMyer *et al.* (1988), who reported reductions in the areas of the right hemisphere as well as left and right frontal cortex, of which only the left frontal area remained significant after controlling for educational level. These studies, together with post-mortem findings (e.g. Bogerts *et al.*, 1985; Brown *et al.*, 1986), also established a greater interest in those parts of the brain that could be considered likely to be involved in schizophrenia, such as frontal and

temporo-limbic structures. Subsequent studies examining such areas of a priori interest have reported statistically significant smaller temporal lobes (DeLisi *et al.*, 1988), particularly on the left (Rossi *et al.*, 1991), or with an abnormal pattern of left-right asymmetries (Johnstone *et al.*, 1989b; Young *et al.*, 1991); an increased VBR (Andreasen *et al.*, 1990) or third ventricle area (Kelsoe *et al.*, 1988); reductions in bilateral (Raine *et al.*, 1992) or left frontal area (DeMyer *et al.*, 1988); as well as reports of smaller thalamic nuclei (Buchsbaum *et al.*, 1996). Some studies have found such abnormalities, of the thalamus (Andreasen *et al.*, 1990) or temporal horns (Johnstone *et al..*, 1989), to be limited to male patients with schizophrenia.

It should be noted however that almost an equally large number of individual reports have not found significant differences in the areas of the temporal lobes (Johnstone *et al.*, 1989; Young *et al.*, 1991; Colombo *et al.*, 1993); the lateral ventricles (Johnstone *et al.*, 1989; Colombo *et al.*, 1993); the frontal lobes (Andreasen *et al..*, 1990; Schwarzkopf *et al.*, 1991; Young *et al.*, 1991); the parietal and occipital lobes (Andreasen *et al.*, 1990), cingulate gyrus (Andreasen *et al.*, 1990; Young *et al.*, 1991); total cerebral or cranial area (Uematsu & Kaiya, 1988b; Andreasen *et al.*, 1990; Schwarzkopf *et al.*, 1991; Aylward *et al.*, 1994); and measures of posterior fossa structures such as the cerebellum and fourth ventricle (Mathew *et al.*, 1985; Nasrallah *et al.*, 1986; Uematsu & Kaiya, 1988b; Andreasen *et al.*, 1990; Aylward *et al.*, 1994). Although these studies do usually find that the structures of interest are smaller in patients with schizophrenia than controls, a reliable quantitative review of these studies - to allow for any Type II error - is not feasible given the varying methods used to identify the areas examined. As already discussed, volumetric studies are more methodologically reliable and comparable, permitting a more reliable quantitative comparison.

1.2.3.4 Volumetric studies

The first MRI study in schizophrenia to include information on structure volumes was published as recently as 1988 by Kelsoe and colleagues at the National Institute for Mental Health in Washington DC (NIMH). They reported a bilateral increase in lateral ventricular volumes of approximately 10ml (62%) that was most marked on the left and posteriorly - at the level of the anterior thalamus; but no significant reductions in the volumes of pre-callosal frontal lobes, temporal lobes, the amygdala-hippocampal complex or cerebral hemispheres. The NIMH group followed this study with a comparison between age and sex matched patients and controls. Temporal lobe volumes were reduced in the schizophrenics by about 15%, with the differences being most apparent in left (21%) and right (18%) grey matter, and particularly the central region containing the amygdala and hippocampus (23%, 20%), while the lateral ventricular volume was substantially (67%) larger (Suddath *et al.*, 1989). In another careful study, these workers provided more evidence for some regional specificity and causes of the brain disturbances in schizophrenia with a comparison between discordant monozygotic twins (Suddath *et al.*, 1990). The affected twins had significantly larger lateral and third ventricles, as well as left and right hippocampi (but not the anterior temporal lobes), such that they could be identified in almost all cases with the naked eye. This result reveals the extent to which many genetic and environmental effects and their interactions determine neural development, and may confound simple case-control comparisons unless some attempt is made to control for them.

Table 1.1 (pp. 23-24) describes these and subsequent MRI case-control studies which have measured the *entire* volume of at least one of the regions they have examined, although many have included some area measurements and/or inadequate coverage of structures of interest (see below). Table 1.1 also includes the matched case-control characteristics in each study for reference to the other tables. Table 1.2 (p.25) lists those studies that have distinguished grey from white matter in the whole brain, pre-frontal and

temporal lobes. Table 1.3 (p.31) details reports giving results for the volume of the pre-frontal and/or temporal lobes and/or smaller components of the mesial temporal lobe; while Table 1.4 (p.38) describes studies of the superior temporal gyrus. In each case, the tables list the numbers of subjects and the percentage differences (rounded to the nearest 0.5% if less than 10% and to the nearest 1% thereafter) between patients and controls in each region for which raw uncorrected volumes are given in the original paper, together with whether these were reported as statistically significant or not. All the figures given refer to patients diagnosed with schizophrenia according to DSM-III or DSM-IIIR criteria.

In addition to considering the varying methods and results of these studies with a traditional 'narrative' review, a quantitative comparison has been made by deriving the median of the percentage differences for each region of interest across methodologically comparable studies (where at least two employed similar methods). Table 1.5 (p.44) shows these median differences across all relevant volumetric studies for each region of interest, according to side and sex where available. In many cases, the largest number of results are given for male patients versus controls, as many studies have only examined such patients as a means of controlling for sex. Studies are included in these median calculations if they measured the entire volume of the structure with the conventional method of isolating the region on single slices - adding these 'areas' together to generate volumes ('serial slice counting'). The reasons for excluding particular studies are given in the text.

For ease of comprehension, this literature review will now discuss all the MRI studies examining particular regions, starting with the cranium and whole brain, followed by the cerebro-spinal fluid (CSF) and ventricular system, and then specific lobar structures.

Table 1.1 - Percentage differences in cranial, cerebral, CSF and ventricular volumes on MRI between patients with DSM-III-(R) schizophrenia and normal controls

Study	N m/f Pts Cls	match	Cranium	Whole Brain	CSF	Lateral Ventricles	Third Ventricle
Kelsoe (1988)	20/4 10/4	-	-	T -0.5 L -0.5 R -0.5	-	T +62* L +66* R +60	-
Suddath (1989)	10/7 10/7	a,s	-	-	-	T +67* L +65* R +67*	-
Andreason (1990)	36/18 28/19	-	-	-	-	(T +31, +43*m, +10f)	T +6, +12m, 0f
Barta (1990)	15/0 15/0	a,s,e, r,p	-	T -2	-	-	-
Bogerts (1990)	22/13 15/10		-	-	-	-	T +35
Dauphinais (1990) analysis #2	15/13 11/10	-	-	-	(L*-3.5m,-5f) (R*-5m, -4f)	(L*+65m,+30f) (R*+29m,+29f)	T +21m, +5f
DeLisi (1991)	9/6 12/8	a	-	T -3	-	L +44* R +28*	T +11
Gur (1991)	27/15 23/20	-	-	(L-2.5m,-2f) (R -2m, -2f)	(L+16m,-5.5f R+17m,-1.5f)	-	-
Jernigan (1991)	28/14 19/5	-	T -2 *f	-	T +20 *m	(T +20, *m)	-
Breier (1992)	29/15 20/9	a,s,p	-	T -2	-	-	-
Degreef (1992)	25/15 15/10	-	-	-	-	L +33* R +21*	T +19*
O'Callaghan (1992)	24/21 14/8	a,s,e	-	-	-	L +31* R +36*	-
Shenton (1992)	15/0 15/0	a,s,h	T +4	-	T -7.5	T +31 *L	T -5
Zipursky (1992)	22/0 20/0	a,s,h	-	-	-	T +34*	-
Harvey (1993)	37/11 19/15	a,e,p	(T-0.5m, -1f)	(T -3m, -2.5f)	(T +35*m, +12f)	(L +2m, +76*f) (R -6m, +22f)	-
Kawasaki (1993)	20/0 10/0	a,s,p	-	L -4.5 R -4.5	-	-	T +25

Study	N m/f Pts Cls	match	Cranium	Whole Brain	CSF	Lateral Ventricles	Third Ventricle
Andreasen (1994a)	36/16 48/42	p	-	(T -3*, -5.5*m, -4*f)	(T+15*, +14*m, +19f*)	(T+20*, +20*m, +12f)	-
Bilder (1994)	39/31 29/22	a,s	-	T -4m,-2.5f L -4m,-3f R-3.5m,-2.5f	-	-	-
Gur (1994)	50/31 50/31	a,s,p	T -3*	T -3.5*	T 0	(T +14*)	-
Marsh (1994)	25/8 27/14	a,s	-	-	-	-	T +52*
Rossi (1994)	19/0 14/0	a,s,h	-	-	-	-	(T +29*)
Schlaepfer (1994)	32/14 43/17	-	-	T -4.5	-	-	-
Zipursky (1994)	22/0 20/0	a,s,h	(T +4)	-	-	-	T +52
Flaum (1995)	70/32 45/42	p	(T -3m -2.5f)	(T -3m -2.5f)	-	T 0m, +24*f L -2.5m,+25f R -2m, +23f	T +20*m, +12*f
Nopoulos (1995)	12/12 12/12	a,s,h, p	-	(T -3)	(T+26*)	(T +22*)	-
Vita (1995)	12/7 9/6	h	-	T -9.5	-	-	-
Fukuzako (1996)	18/0 18/0	a,s	-	L -1.5 R -3.5	-	-	-
Kulynych (1996)	12/0 12/0	s,h	-	T -1.5	-	-	
Lim (1996)	22/0 24/0	a	(T -2)	-	-	(T +34*)	(T +55*)

Key: N number of, m/f male/female, Pts patients and Cls controls; match(ed) for: a - age, s - sex, h - handedness, e - educational level, r - race, p - paternal occupation or social class; T total, L left, R right; * reported as statistically significant difference in original paper ('x') figures in brackets not included in median calculations due to methodological differences (see text for further details).

Note: A further 9 volumetric MRI studies (to the 29 in Table 1.1) are in the literature. However, these are excluded due to: incomplete temporal 'volumes' (Rossi, 1991); different scan sequences in cases/controls (Shenton, 1991); same cerebral volume data (Noga, 1994; Menon, 1995) as a previous study (Barta, 1990); or are described in Tables 1.2 (Wible, 1995), or 1.3 (Becker, 1990; Swayze, 1992; Bogerts, 1993; Turetsky, 1995), or 1.4 (Menon, 1995) - see text for further details. Figures quoted for DeLisi, 1991 refer only to chronic cases as several first onset were later described as schizo-affective.

Table 1.2 - Segmentation studies of percentage differences in regional grey and white matter between DSM-III-(R) schizophrenia and normal controls

Study	Pts m/f Cls m/f matching	Whole Brain grey	Whole Brain white	Pre-Frontal grey	Pre-Frontal white	Temporal Lobe grey	Temporal Lobe white
Suddath (1989)	10/7 10/7 a,s	-	-	L -5.5 R -7	L -1.5 R +4.5	L -21* R -18*	L +1 R -11
Breier (1992)	29/15 20/9 a,s,p	-	-	L 0 R -4	L -12* R -16*	-	-
Shenton (1992)	15/0 15/0 a,s,h	+2	+7	-	-	-	-
Zipursky (1992)	22/0 20/0 a,s,h	-7*	-	-	-	-	-
Harvey (1993)	37/11 19/15 a,e,p	(-4m, -4.5f)	(-2.5m, -1f)	-	-	L -1.5m, -1.5f R -5m,-6f	L-2.5m,-5f R -5.5m, -14f
Schlaepfer (1994)	32/14 43/17 -	-4.5	-	-	-	-	-
Zipursky (1994)	22/0 20/0 a,s,h	-	-	-	-	(L -2.5*) (R -0.5*)	(L +10) (R +10)
Menon (1995)	20/0 20/0 a,s,e,r,p	-	-	-	-	-	-
Wible (1995)	14/0 15/0 a,s,h,p,IQ	-	-	L -3.5 R -2.5	L +2.5 R +1.5	-	-

Key: N number of, m/f male/female, Pts patients and Cls controls; match(ed) for: a - age, s - sex, h - handedness, e - educational level, r - race, p - paternal occupation or social class; T total, L left, R right; * reported as statistically significant difference in original paper ('x') figures in brackets do not include the whole volume of the structure (see text for further details).

(i) The intracranial and whole brain volumes

Most of the eight studies examining the volume of the cranial vault in schizophrenics and controls have reported non-significant differences, and three studies have actually identified a small increase in the size of the cranium in males (Shenton *et al.*, 1991 & 1992; Zipursky *et al.*, 1994). Nonetheless, the single largest sample (Flaum *et al.*, 1995), the two studies that report statistically significant differences (Jernigan *et al.*, 1991; Gur *et al.*, 1994), and the two that have given values for men and women individually (Harvey *et al.*, 1993; Flaum *et al.*, 1995) all suggest the cranium is smaller in patients with schizophrenia, at least in women. This possible sex difference is shown in the median values from the two studies of the entire cranial vault in both sexes, as shown in Table 1.5 (p.44), where (excluding the Harvey, Zipursky, Flaum and Lim studies which did not cover the whole structure, as well as the 1991 Shenton study which used different scan sequence in cases and controls) the median difference is -2.5% for schizophrenics overall, but +4% for men in the single comparable study (Shenton et al., 1992).

The figures for the volume of the whole brain and the cerebral hemispheres are more consistent. Seventeen independent studies report volume reductions, including first episode cases (DeLisi *et al.*, 1991; Nopoulos *et al.*, 1995), with only one exception (Shenton *et al.*, 1991), although these were only significant in three relatively large series (Zipursky *et al.*, 1992; Andreasen *et al.*, 1994; Gur *et al.*, 1994) and one further study which only included the anterior portion of the brain (Dauphinais *et al.*, 1990). Small reductions have also been found with segmentation (Gur *et al.*, 1991), or automated methods (Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995). The median figures from slice counting studies show a reduction of 3.25% in the whole brain volume in both sexes (six studies), and of 4% in men and 3.25% in women individually, with similar reductions in the left and right hemispheres in men (see Table 1.5) - with similar results in studies which excluded inferior (Flaum) or posterior (Harvey) portions. This deficit appears to be largely a loss of grey matter (median 4.5%), as white matter may be increased (Table 1.2).

(ii) Cerebro-Spinal Fluid (CSF)

Such a loss of whole brain volume, with a lesser reduction or even an increase in the cranial volume, suggests that the amount of CSF will be increased in schizophrenia although relatively few (eight) studies have examined this issue. Four studies have reported significant increases in men (Jernigan *et al.*, 1991; Harvey *et al.*, 1993), both men and women (Andreasen *et al.*, 1994a) and in first episode cases (Nopoulos *et al.*, 1995). Gur *et al.* (1991) reported small reductions in CSF in women, with 16-17% increases in men and a significant increase in sulcal CSF: brain ratio in men. However, they found that the whole brain reduction equalled that of the cranium in a later study (Gur *et al.*, 1994); while the small studies of men from Harvard have reported an atypical picture of larger craniums and smaller amounts of subarachnoidal CSF (Shenton *et al.*, 1991 & 1992). Taken together, the median value for total CSF is of a 10% increase overall (two studies), with only one slice counting study giving results for men (Shenton *et al.*, 1992) and none for women. The automated studies, however, report larger increases and particularly in men (Gur *et al.*, 1991; Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995), as do Harvey *et al.* (1993).

There is very limited information available about any regional variation in the putative increase in CSF volumes, but Harvey and co-workers (1993) also examined the Sylvian fissures and did find significant differences in both sexes and on both sides - with particular increases on the left in men (48%/37%) and on the right in women (34%/45%). Andreason *et al.* (1994a) used an automated method to establish regional CSF volumes and found that the increase was most marked in fronto-temporal regions, as did Lim *et al.* (1996), while another study found significantly increased temporal but not frontal CSF (Turetsky *et al.*, 1995). One qualitative MRI study used the protocol established by the Consortium for Alzheimer's Disease and found that general atrophy ratings for both the Sylvian fissures were significantly increased in schizophrenia, with non-significantly increased atrophy in temporal lobe and superficial cerebral sulci (Schwartz *et al.*, 1992).

(iii) The ventricular system

Following on from the CT findings, the ventricular system has been examined in more MRI studies than any other region and there can be little doubt that there is a dramatic increase in the volume of the ventricles in schizophrenia. Four groups have reported increased volumes of the entire ventricular system with various methods (Jernigan *et al.*, 1991; Andreasen *et al.*, 1994a; Gur *et al.*, 1994; Nopoulos *et al.*, 1995). Taking the lateral ventricles alone, all thirteen studies to date has found significant volume increases - with only one exception (Shenton *et al.*, 1991). The pattern of these differences varies amongst studies, with some reporting significance on only the left side (Kelsoe *et al.*, 1988; Shenton *et al.*, 1992), or in women (Flaum *et al.*., 1995), but most studies reporting no significant sex or laterality differences (e.g. O'Callaghan *et al.*, 1992). Excluding those that did not cover all the ventricles posteriorly (Andreasen *et al.*, 1990; Dauphinais *et al.*, 1990; Harvey *et al.*, 1993; Lim *et al.*, 1996), the overall median ventricular volume increase is by 64% in total, and by 44% on the left and 36% on the right (see Table 1.5 on p.44). The only study to examine sex differences in the entire structure has found that the changes are minimal in men and much greater in women (Flaum *et al.*, 1995). This result, from the largest MRI study in schizophrenia to date, challenges earlier results suggesting greater changes in men (Andreasen *et al.*, 1990; Harvey *et al.*, 1993). However, in the three studies giving figures for men alone, the median total increase is of 31% (Shenton *et al.*, 1992; Zipursky *et al.*, 1992; Flaum *et al.*, 1995), as compared to 24% in a single study of women (Flaum *et al.*, 1995).

Several groups have also reported data on sub-divisions of the lateral ventricles. Some have found the frontal horns to be most enlarged (Andreasen *et al.*, 1990), others the temporal horns (Kawasaki *et al.*, 1993), or even the occipital horns (Vita *et al.*, 1995). However, the largest differences are for the body of the lateral ventricles where every results has been statistically significant (40% on the left, and 33% on the right, Degreef *et*

al., 1992; 50/75%, Kawasaki *et al.*, 1993; 58/68%, Zipursky *et al.*, 1994; 59/61% Vita *et al.*, 1995 - medians, from two studies each, of 50/47% overall and 54/72% in men).

Seven studies have reported measures of the temporal horn volume, with four reporting statistically significant increases of as much as 200% on the left and 74% on the right in men alone (12/11%, Becker *et al.*, 1990; 180/74%, Shenton *et al.*, 1992; 200/50%, Kawasaki *et al.*, 1993) or in both sexes (21/13%, Degreef *et al.*, 1992), with three studies finding non-significant differences (18/14%, DeLisi *et al.*, 1991; 55/65%, Zipursky *et al.*, 1994; 2/-1%, Vita *et al.*, 1995). Thus, the median increase is of 18% on the left and 13% on the right side in the three studies to examine both sexes together (Degreef, DeLisi, Vita). In the four studies examining the sexes individually, Bogerts *et al.*. (1990) found general increases, but these were only significant for the left side in women (15/10% male, 32/9% female); Dauphinais *et al.* (1990) reported small increases that were most marked on the left in women and the right in men (-7.5/10% men, 10/5% women); while Flaum *et al.* (1995) found smaller increases in men on both sides (3/2.5% and 17/11% respectively). Only one study has reported increases that were greatest in men, but there was no diagnosis-side interaction and no specific figures for the sexes were given (Degreef *et al.*, 1992). Thus, the evidence (medians of 15/11% increases in men and 17/11% in women) does not strongly support the often reported impression of greater abnormalities in men although the increases do appear larger on the left side in both cases.

Four studies give figures for the frontal horns of the lateral ventricle (+15% left, +2.5% right, Delisi *et al.*, 1991; 35/24%, Degreef *et al.*, 1992; 22/23% in men, Kawasaki *et al.*, 1993; -8.5/+2%, Vita *et al.*, 1995). Again, overall enlargement is evident (median left 15%, right 2.5%), with some suggestion of leftward laterality (see Table 1.5). Similar conclusions can be drawn from the three studies reporting on the volume of the occipital horns (30/14%, Degreef *et al.*, 1992; 24/35%, Kawasaki *et al.*, 1993; 32/41%, Vita *et al.*, 1995).

The final component of the ventricular system to receive concentrated attention has been the third ventricle (see Table 1.1). Eleven volumetric studies have been conducted, five of which reported significant increases (Degreef *et al.*, 1992; Marsh *et al.*, 1994; Flaum *et al.*, 1995) although two of these did not cover the full length (Rossi *et al.*, 1994) or depth of the structure (Lim *et al.*, 1996). The median increases are of 19% overall, and more so in men (21%) than women (5%). One study reported a small reduction in the volume of third and fourth ventricles combined (Shenton *et al.*, 1991), while two studies have found a small increase (8%, Degreef *et al.*, 1992) or decrease (12%, Shenton *et al.*, 1992) of the fourth ventricle itself.

In summary, there is convincing evidence that the volume of the lateral ventricle, and to a lesser extent the third ventricle, is substantially increased in schizophrenia, with the body of the lateral ventricle enlarged by about 50%. The temporal, frontal and occipital horns are also increased, by about 15%, 15% and 30% respectively, with a possible leftward laterality. However, there is less certainty that these figures can be reliably compared as few reports explicitly reported that they examined the whole volume of these sub-divisions or gave their anatomical boundaries as the ventricles have "naturalistic boundaries'. Finally, there is some evidence for the presence of greater abnormalities in male patients, but as with much of the brain imaging literature in schizophrenia relatively few female patients have been scanned. This review will now turn to putative abnormalities in particular brain regions, starting with the frontal lobes.

Table 1.3 - Percentage case/control differences of lobar structures in schizophrenia.

Study	Pts m/f Cls m/f	Pre-Frontal Lobe	Temporal Lobe	Amygdala-Hippocampus	Amygdala (alone)	Hippocampus (alone)
Kelsoe (1988)	20/4 10/4	L 0 R -1.5	L -6 R -9.5	L -12 R -15	-	-
Suddath (1989)	10/7 10/7	L -3.5 R -1	L -13 R -15	(L -20*) (R -23*)	-	-
Becker (1990)	10/0 10/0	-	(L -1.5) (R -4.5)	-	-	L -6 R -9
Bogerts (1990)	22/13 15/10	-	L -5m, +5f R -9*, -2f	L -9*m, +2f R -9*m, -1f	L+15m+5f R-10m-11f	L-20m*,+1f R-8m, +7f
DeLisi (1991)	9/6 12/8	L -7.5 R -7	L -11 R -10	L -4.5 R -2	-	-
Breier (1992)	29/15 20/9	L -7.5* R -10.5*	-	L -9* R -9*	L -12* R -18*	L -8* R -5*
Shenton (1992)	15/0 15/0	-	-	L -6.5* R -4.5	L -21* R not given!	L not given! R not given!
Swayze (1992)	36/18 28/19	-	T+3.5l+2.5r L+3.5m,+2f R+0.5m,+5f	T+2.5l, +2.5r L+0.5m,+4.5f R+1.5m,+2f	-	(T 0 l, -3r) (L 0m, +1.5f) (R 0m, -10f)
Bogerts (1993)	19/0 18/0	-	-	L -11* R -12*	L +5 R -7	L -20* R -15*
Kawasaki (1993)	20/0 10/0	L -15 R -9.5	L -1.5 R -0.5	-	L -10 R -10	(L +5.5) (R +10)
Andreasen (1994a)	36/16 48/42	(T -5*, -6*m,-7.5*f)	(T -2.5*, -0.5*m, -2f)	-	-	-
Bilder (1994)	39/31 29/22	L -2m,+0.5f R -5.5m,-5f	L -3m,-4.5f R -7m,-3.5f	-	-	-
Rossi (1994)	19/0 14/0	-	-	-	L -18* R -11	(L -3*) (R -4)
Zipursky (1994)	22/0 20/0	-	(L +1.5) (R + 3)	-	-	L +1 R -1.5
Flaum (1995)	70/32 45/42	-	T -2.5m,-4.5f L -1m, -5f R-3.5m,-4.5f	-	-	T -2m,-9.5*f L 0m,-7.5f R -3.5m,-12f
Nopoulos (1995)	12/12 12/12	(T -5*)	(T -2)	-	-	-
Turetsky (1995)	44/27 48/29	(L -3m, -2f) (R-3.5m,-3f)	(L -5m, -2f) (R -3.5m, -1f)			
Vita (1995)	12/7 9/6	L +2.5 R +2	L +2.5 R 0	-	-	-
Fukuzako (1996)	18/0 18/0	-	-	-	-	L -8* R -11*

Note: Barta, 1990; Dauphinais, 1990; Rossi, 1991& 1994; Marsh, 1994 excluded (see text)

(iv) Frontal lobes

The increased resolution of MRI has allowed researchers to examine the suggestions from CT studies that the frontal lobes are reduced in size. Most of the ten MRI studies have employed a serial slice counting technique from the frontal pole to the genu of the corpus callosum, although others have used the optic chiasm as the posterior boundary (DeLisi *et al.*, 1991) and some have used alternative methods. The Iowa group have allocated pixels to lobes and automatically derived volumes thereafter (Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995), while workers in Philadelphia first isolate the frontal (and temporal) lobes on axial slices (Turetsky *et al.*, 1995). Although only three studies have described significant reductions of the whole pre-frontal lobe volume (Breier *et al.*, 1992; Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995), the median reductions over five comparable studies in both sexes are of 3.5% and 1.5% in the left and right hemispheres respectively. Although the differences may be of about 8% in males (Kawasaki *et al.*, 1993; Bilder *et al.*, 1994), the overall figures are no greater than those for the whole brain - contrary to the early findings of the Iowa group (Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995). Three studies in total have segmented the pre-frontal lobe into grey and white matter and suggest that the volume deficit is largely attributable to the former (see Table 1.2). Wible *et al.* (1995) examined only male subjects and found reductions of about 3% in grey matter, with smaller increases in white matter, that were greater (up to 7%) after correcting for intracranial volume.

Thus, although some researchers have found that volume deficits in the pre-frontal lobes are greater than those in the whole brain, the balance of the evidence does not support this view - except, possibly, in men. Similarly, some authors have reported that the frontal lobe deficit is greater than or equal to temporal lobe reductions (Kawasaki *et al.*, 1993; Andreasen *et al.*, 1994a; Flaum *et al.*, 1995; Nopoulos *et al.*, 1995; Turetsky *et al.*, 1995; Vita *et al.*, 1995), but the MRI studies of the temporal lobes and constituent parts provide the strongest evidence for abnormalities of brain structure in schizophrenia.

(v) Temporal Lobes

A total of sixteen studies have examined the volume of temporal lobe itself and the vast majority have matched for at least age and sex. The structure has been taken as stretching from the temporal pole back approximately 60mm to the colliculi (Kelsoe *et al.*, 1988; Vita *et al.*, 1995) or the auditory canal (DeLisi *et al.*, 1991); 70mm to the last slice containing the Sylvian fissure (Suddath *et al.*, 1989; Harvey *et al.*, 1993; Flaum *et al.*, 1995) or to where the fornix forms the medial wall of the lateral ventricle (Bogerts *et al.*, 1990) or to the splenium (Bilder *et al.*, 1994); and even 80mm until the appearance of the posterior horn of the lateral ventricle (Kawasaki *et al.*, 1993) - measurements taken from Duvernoy (1991). Although Zipursky *et al.* (1994) used the latter posterior definition, neither they nor Becker *et al.* (1990) included the poles. Other methods have been used as described for the frontal lobes (Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995; Turetsky *et al.*, 1995). Some researchers have simply allocated a certain number of slices to be measured, but only one has included sufficient slices to cover a comparable amount of the structure (50-60mm, Swayze *et al..*, 1992). Not included in Table 1.3, or the median calculations, are two studies which used an insufficient number of slices to cover the structure - both of which found significant differences, of 7-11%, in nine 3mm thick slices (Barta *et al.*, 1990), or three 10mm slices (Dauphinais *et al.*, 1990).

Despite these varying methods some consensus has been achieved, although only a minority of studies have shown statistically significant differences (Bogerts *et al.*, 1990; Andreasen *et al.*, 1994a; Nopoulos *et al.*, 1995). Early studies reported non-significant reductions of 10-15% (Kelsoe *et al.*, 1988; Suddath *et al.*, 1989; DeLisi *et al.*, 1991), which have been confirmed in first episode cases (Bogerts *et al.*, 1990) and do not appear to progress (DeLisi *et al.*, 1992). The median reduction across the five slice counting studies reporting in both sexes is of 6% on the left and 9.5% on the right, without any apparent difference according to posterior boundary (see Tables 1.3 and 1.5). For the sexes individually, however, the median reductions are in the order of 2-3% which is

similar to the figures from automated methods and no greater than that for the whole brain; although fewer studies are included in this estimate and it is therefore less reliable.

There are again suggestions from segmentation studies that these volume reductions are attributable to grey matter loss (Suddath *et al.*, 1989; Zipursky *et al.*, 1994). Jernigan *et al.* (1991) reported a reduced 'inferior-anterior' cortical volume, which included mesial temporal and orbitofrontal regions, that was most apparent in men, while Lim *et al.* (1996) found grey matter deficits in frontal, temporal and parietal regions that were most marked fronto-temporally. However, one study reported reductions in both grey and white matter (Harvey *et al.*, 1993), and Schlaepfer *et al.* (1994) examined heteromodal association cortex and found significant reductions that were no greater than generalised grey matter deficits (of 4.5%).

Taken together, there is some evidence that the temporal lobes are preferentially affected in schizophrenia, but this is not as convincing as the results from studies that have examined individual anatomical components of the temporal lobe.

(vi) Amygdala-Hippocampal Complex

These structures have been of particular interest to schizophrenia researchers since a number of post-mortem studies suggested that they may be preferentially affected (e.g. Bogerts *et al.,* 1985; Brown *et al.,* 1986). The NIMH workers were the first to report reductions in such mesial structures on MRI (Kelsoe *et al.,* 1988), and they have now been examined in a total of 17 MRI studies, which have taken a number of methodological approaches.

Ten published papers have examined the entire amygdala-hippocampal complex (see Table 1.3), seven of which reported statistically significant reductions that have usually been evident bilaterally. Again, some have attempted to do so without sufficient coverage of a structure that is at least 50mm long in the coronal plane (Duvernoy, 1990). Suddath *et al.* (1989) described substantial reductions, but in only one of three single 10mm slices; Dauphinais *et al.* (1990, analysis#2) found differences of 7-14% that were significant on the right side in male subjects but only used two 10mm slices; and Marsh *et al.* (1994) again examined two 10mm sections and reported significant reductions of 12-14%. However, four of the seven studies which did include all the complex, with the same anatomical definitions as for the temporal lobe, have also found statistically significant reductions (the figures for the study of Shenton *et al.* 1992, being given in McCarley *et al.,* 1993). The median reductions are of about 6% overall, with the possibility that the differences are largely attributable to men (about 7%) rather than women who show small increases (see Table 1.5). Additional information has been given by some research groups on the volumes of amygdala and/or hippocampus and/or parahippocampal gyrus individually.

(vii) Amygdala

Six studies have examined comparable volumes of the amygdala in isolation, although this has been measured in both sexes together (Breier *et al.*, 1992) or individually (Bogerts *et al.*, 1990) in only one study each. Again, a variety of ways of delineating the structure have been employed. Some workers have simply measured the structure on a set number of slices, which have given sufficient (2x10mm, Kawasaki *et al.*, 1993; 2x5mm, Rossi *et al.*, 1994) or insufficient coverage (2x3mm, Barta *et al.*, 1990), or only an area rather than a volume (1x10mm, Suddath *et al.*, 1989; Swayze *et al.*, 1992; Marsh *et al.*, 1994). Others have arbitrarily separated amygdala from hippocampus as anterior and posterior, respectively, to the mammillary bodies (Bogerts *et al..*, 1990 & 1993; Shenton *et al.*, 1992) or excluded this transition area from the measures (Breier *et al.*, 1992). Four of the six comparable studies only examined male subjects, with two of them and one of the other reports finding significant reductions on only the left side (Barta *et al.*, 1990; Shenton *et al.*, 1992; Rossi *et al.*, 1994). However, two of the studies using internal landmark boundaries actually found increases on the left side in men (Bogerts *et al..*, 1990 & 1993), suggesting that the results are dependent on methodological or population differences. Furthermore, the fact that Shenton *et al.* (1992) do not give a figure for the non-significant difference on the right side suggests that publication bias may be operating in these figures. The median calculation can only be made for men but suggests a large and bilateral reduction in the volume of the region of about 10%.

(viii) Hippocampus

Seven comparable studies have examined the entire hippocampus (see Tables 1.3 and 1.5). Most have only examined male subjects, but one gave figures for both sexes together (Breier *et al.*, 1992) and two studies give results for either sex - with conflicting results as to whether men or women show the greatest reductions (Bogerts *et al.*, 1990; Flaum *et al.*, 1995). The hippocampus has been distinguished from the amygdala arbitrarily (Bogerts *et al.*, 1990 & 1993; Breier *et al.*, 1992), by a set number of slices (7x4mm, Becker *et al.*, 1990), or by visual tracing (Zipursky *et al.*, 1994; Flaum *et al.*, 1995; Fukuzako *et al.*, 1996). Five of these studies have reported significant volume reductions, most commonly on the left side in men. Excluding studies which did not include anything approaching the whole volume (2x10mm, Swayze *et al.*, 1992; 2x10mm, Kawasaki *et al.*, 1993; 2x5mm, Rossi *et al.*, 1994; 1x10mm, Marsh *et al.*, 1994), the median reductions are 7-8% in men (six studies) and 2-3% in women (two studies). These findings are complemented by a report that visual inspection of the pes hippocampus could distinguish cases from non-cases in most monozygotic twin pairs (Suddath *et al.*, 1990).

(ix) Parahippocampal Gyrus

A small number of studies have examined the volume of the parahippocampal gyrus. In each case, the structure has been visually isolated in slices covering the entire temporal lobe. Reductions on the left side have been equal to or greater than those on the right (-4.5/-1%, Becker *et al.*, 1990; -10/-10%, DeLisi *et al.*, 1991; -14/-9%, Shenton *et al.*, 1992; -15/-10% Kawasaki *et al.*, 1993), with five of these eight differences being statistically significant. The median reductions in men (three studies) are therefore -14% on the left and -9% on the right, which are the greatest cortical reductions in the literature (see Table 1.5). It is however conceivable that these results are skewed by selective reporting of significant results. The final component of the temporal lobe of interest to schizophrenia researchers is the superior temporal gyrus (STG, see Table 1.4 overleaf).

Table 1.4 - Volumetric MRI studies of the STG in DSM-III-(R) schizophrenia, with percentage differences from controls (and approximate volumes for comparison)

Study	Pts m/f Cls m/f	match	Methods	STG ANT.	STG MID.	STG POST.	STG TOTAL
Barta (1990)	15/0 15/0	a,s,e,p r, (h)	1.5T, 3mm thick, 3 slices - two with amygdala plus 1 slice posterior	L -11* R -13* (~2ml)	-	-	-
Shenton (1992) and McCarley (1993)	15/0 15/0	a,s,h	1.5T, 1.5mm thick, ant. - temp.stem to 1 slice ant to mam. body post. - mam. body to crux fornicis	L -33* R not given! (~1ml)	-	L -14* R not given! (~5ml)	L -15* R 0 (~6ml)
DeLisi (1994b)	50/35 24/16	a,s,sc, (h)	1.5T, 5mm+2mm gap, ant.-3 slices from temp. pole tot.- 7-8 slices in total	L 0m, L -5.5f* R -3m R -6.5f* (~5-6ml)	-	-	L +1.5m L -5.5f, R -2.5m R -5.5f (~13ml)
Zipursky (1994)	22/0 20/0	a,s,h	1.5T, 3mm slices, temp.stem to 1 slice before fornix (blind to side)	-	-	-	L 0 R +2.5 (~10ml)
Flaum (1995)	70/32 45/42	p, (a,h)	1.5T, 3mm + 1.5mm gaps, temp. pole to loss of visible Sylvian fissure	-	-	-	L -3.5m L -9f R -5.5m R -6f (~13ml)
Menon (1995)	20/0 20/0	a,s,r,e, p (h)	1.5T, 3mm slices, mid.-3 slices, pons+/-1 post.-3 slices,splenium plus 2 anteriorly Adjusted for tilt	-	L -3 R -5 (~3ml)	L -11 R +2 (~3ml)	-
Vita (1995)	12/7 9/6	h	0.5T, 5mm +2mm gap, post. - colliculi and three anterior slices	-	-	L +4.5 R -2 (~8ml)	
Kulynych (1996)	12/0 12/0	s,h (a)	1.5T, 1.5mm slices, as Shenton, 1992 [c.f. surface rendering] (blind to side)	L +9.5 R +3 (~3ml)	-	L -6 R -3 (~16ml)	L-2.5[-12] R-2 [0] (~19ml)

Key: Number of male/female (m/f) patients (Pts) and controls (Cls); match - matched or (almost identical) for a-age, s-sex, h-handedness, r-race, e-education, p-paternal social class, sc-social class; ant-anterior, mid-middle, post-posterior, tot-total, mam.-mammillary body, temp.- temporal.; *significant in original paper. Note: Approximate volumes are given in brackets for comparison; the Shenton (1992) study was of grey matter only.

(x) Superior Temporal Gyrus (STG)

Barta *et al.* (1990) were the first to examine this component of the temporal lobes and reported significant reductions in the (anterior) volume of the structure. Subsequent studies (see Table 1.4) have provided a confusing array of results, due to varying methods, as demonstrated by the substantially different volumes derived. Shenton *et al.* (1992) reported significant reductions in the amount of *grey matter* in all three components they measured, without giving figures for the non-significant differences on the right side although one of these can be found in McCarley *et al.* (1993). DeLisi *et al.* (1994) found reductions in first episode cases, that were significant for women, but included an unspecified schizoaffective patients in their sample. Other workers have reported non-significant differences in parts of or the whole gyrus (see Table 1.4). Although differing boundary definitions limit the comparability of these studies, it can be seen from the Table that median differences for the anterior STG would be small and, if anything, greater on the right side and in women (see DeLisi *et al.*, 1994b). Values for the middle and posterior portions are too few and varied to allow a reliable comparison. The differences for the whole STG are perhaps in the region of -2% in men and -6% in women, with no substantial laterality. Kulynych *et al.* (1996) also compared results from the standard serial slice measurements with surface rendering techniques. They found small reductions (of about -2%) using the standard approach, which were only evident posteriorly, but much greater differences with the newer technique (-12%) that were limited to the left side. The NIMH group have also reported non-significant surface area reductions of the planum temporale (PT, -1.5/-7.5%) and increases in Heschl's gyrus (HG, +7.5/8%), in the middle and posterior portions of the STG respectively, with surface rendering (Kulynych *et al.*, 1995).

However, the segmentation studies that have discriminated grey from white matter in the STG have delivered a much more consistent pattern of results. Grey matter reductions, at least in male patients, are apparent in the anterior (-33%, Shenton *et al.*,

1992), middle (-20 left/-26% right, Menon *et al.*, 1995), and posterior (-14%, Shenton *et al.*, 1992; -24/-11%, Menon *et al.*, 1995) portions, as well as in the whole STG (-15%, Shenton *et al.*, 1992; -5/+1%, Zipursky *et al.*, 1994), with only the latter study failing to find statistically significant differences. These differences are also most pronounced on the left side in most regions. The only report to include an examination of white matter in the STG has found it to be non-significantly increased by 9-10% (Zipursky *et al.*, 1994).

The STG, PT and HG are highly functionally specialised and lateralised, and have therefore been most closely examined for the putative abnormality in cerebral asymmetry in schizophrenia.

(xi) Cerebral Asymmetry

Although many research groups have not found any evidence of cerebral asymmetry, in terms of diagnosis by side interactions, in a variety of brain structures in patients with schizophrenia (Suddath *et al.*, 1989; Dauphinais *et al.*, 1990; DeLisi *et al.*, 1991 & 1992; Zipursky *et al.*, 1994; Flaum *et al.*, 1995), it is noticeable that many of the regional volumetric reductions are most pronounced on the left side (see Table 1.1). For example, the Harvard group have reported more marked reductions in the left lateral ventricle (Shenton *et al.*, 1991) and mesial temporal lobe structures (Shenton *et al.*, 1992), and workers in Philadelphia have found greater deficits in the left rather than the right temporal lobes in patients as compared to controls (Turetsky *et al.*, 1995). These impressions are strengthened by many of the median figures (see Table 1.5), particularly for ventricular structures. It should be noted, however, that the left lateral ventricle and the right temporal lobe are larger than their contralateral partners in normal controls (Jack *et al.*, 1988) and these results may therefore reflect an excess of asymmetry rather than any reduction or reversal. Nonetheless, the fact that many of the median reductions are more marked in temporal structures on the right does support the asymmetry hypothesis

The most systematic attention to this issue has been through studies of cerebral 'torque'. In normal subjects, the right frontal and left occipital lobes are relatively larger than their left and right sided equivalents whereas some CT studies suggested that this difference was reduced or even reversed in patients with schizophrenia. Thus far, three MRI studies have addressed this phenomenon with the necessary explicit correction for any tilt or rotation of the cranium in the scanner. Bilder and colleagues (1994) found reduced asymmetries in frontal and occipital regions in first episode patients, which was associated in post hoc tests with paranoid sub-type and negative symptoms in men. Zipursky *et al.* (1994) however, found no evidence for this loss of torque, whereas Turetsky *et al.* (1995) did find reduced torque in the frontal and temporal lobes.

More studies have examined the smaller components of the temporal lobe - the planum temporale (PT), Heschl's gyrus (HG) and the superior temporal gyrus (STG) - in the search for abnormalities of asymmetry. These structures are intimately associated with language functions and are normally larger on the left side. The planum temporale has been reported as showing less asymmetry in schizophrenics (Rossi *et al.*, 1992 & 1994; DeLisi *et al.*, 1994), or only in females with schizophreniform psychosis (Hoff *et al.*, 1992), or no significant difference (Bartley *et al.*, 1993; Kleinschmidt *et al.*, 1994). One group has also reported reversed asymmetry (right larger than left) of the PT but not of the HG (Petty *et al.*, 1995). DeLisi *et al.* (1994) and Menon *et al.* (1995) have found no diagnosis by side interaction in STG volumes. These discrepancies clearly indicate methodological problems. Laterality is influenced by handedness and gender, which are not always adequately controlled; raters are generally not blind to the side of the brain they are examining; and 'asymmetry quotients' may not control for overall brain size differences (Bullmore *et al.*, 1995), particularly if any head tilt is uncorrected (Zipursky *et al.*, 1991). NIMH workers have been the first to deal with these issues and found no evidence for reversed asymmetry of the PT or HG (Kulynych *et al.*, 1995), and only found some in the STG on measurement with the more reliable surface rendering (Kulynych *et al.*, 1996).

(xii) Other cortical structures

Morphometric studies have concentrated on the frontal and temporal lobes, but several researchers have also examined other regions although they generally report less substantial or significant differences. In Iowa, Andreasen *et al.* (1994a) found brain tissue deficits were generalised to all lobes in males (albeit by only about 3%) but only to frontal lobes in females, and volume reductions were not found in parietal and occipital lobes in first episode patients (Nopoulos *et al.*, 1995). Bilder *et al.* (1994) did find significant reductions in the occipito-parietal lobes, particularly on the left side in women (-11%), and of the premotor cortex but not the sensorimotor areas. The cerebellum has also been shown to be smaller in patients than in controls, again particularly in females, in two studies (Andreasen *et al.*, 1994a; Flaum *et al.*, 1995), as have the cingulate gyrus (Noga *et al.*, 1995) and pineal gland (Rajarethinum *et al.*, 1995) in one study each, but the reductions have been small and apparently no greater than that of the brain in general (3-5%).

(xiii) Thalamus and Basal Ganglia

In 1994, the Iowa group published the results of the innovative analysis technique of brain averaging, which identified smaller volumes of the thalamus and adjacent white matter (Andreasen *et al.*, 1994b). However, such putative abnormalities may be no greater than those expected due to a general reduction in brain volumes as found in the only other pertinent study (-2.5%, Jernigan *et al.*, 1991). Such mesial effects could also be attributable to compressing the image of smaller schizophrenic brains 'on average' and awaits independent replication, although the Iowa workers have internally replicated their result with a standard serial slice analysis (6-7% smaller bilaterally, Flaum *et al.*, 1995).

In contrast to the volumetric reductions in cortical regions, the most persuasive evidence of abnormalities in subcortical nuclei is for volume *increases* with time and exposure to antipsychotic medication. Kelsoe *et al.* (1988) found increased areas of the

pallidus and putamen, but the first volumetric study of the basal ganglia (DeLisi *et al.*, 1991) reported 2.5-4% increases in caudate and lenticular nuclei volumes in chronic hospitalised patients as compared to controls. These results have been supported by subsequent findings of increased lenticular nuclei volumes, more so on left and in early onset subjects (Jernigan *et al.*, 1991), putamen (and lesser caudate) enlargement in young chronic male patients (Swayze *et al.*, 1992), larger caudate volumes in both deficit and non-deficit patients (Buchanan *et al.*, 1993), bilateral pallidal and right putamen increases in chronic cases (Elkashef *et al.*, 1994), and an increase in all components of the basal ganglia in schizophrenia (Hokama *et al.*, 1995) - although some studies have reported small reductions in caudate volume (Jernigan *et al.*, 1991; Flaum *et al.*, 1995). Most persuasively, volume increments of 6% (Chakos *et al.*, 1994) and 15% (Keshavan *et al.*, 1994) have been observed in first episode and neuroleptic naive patients respectively over one year to eighteen months of treatment. These increases showed a dose response relationship with typical antipsychotics (Chakos *et al.*, 1994), but reversed on treatment with clozapine (Chakos *et al.*, 1995), suggesting that D2 receptor blockade is responsible. Such normalisation with clozapine treatment has also been described in childhood onset cases of schizophrenia (Frazier *et al.*, 1996), although a relationship has not been found with tardive dyskinesia in adults (Elkashef *et al.*, 1994). This sensitivity to medication effects over a relatively short period of time suggests that prospective cohort studies could determine whether the regional brain volume abnormalities in patients with schizophrenia summarised in Table 1.5 (overleaf) are static and therefore neurodevelopmental or progressive and probably neurodegenerative.

Table 1.5 - Median percentage differences in MRI volumes from studies using comparable methods (N, range of results) in patients with schizophrenia.

REGION	BOTH SEXES	MEN	WOMEN
Cranium	-2.5 (2, -3 to -2)	-	-
Whole Brain	-3.25 (6, -9.5 to -0.5)	-4 (5, -7 to -1.5)	-3.25 (2, -4 to -2.5)
Left Hemisphere	-	-4 (3, -4.5 to -1.5)	-
Right Hemisphere	-	-4.5 (3, -4.5 to -3)	-
Cerebro-Spinal Fluid	+10 (2, 0 to +10)	-	-
Lateral Ventricle (LV)	+64 (2, +62 to +67)	+31 (3, 0 to +34)	-
Left LV	+44 (5, +31 to +66)	-	-
Right LV	+36 (5, +21 to +67)	-	-
LV body - Left side	+50 (2, +40 to +49)	+54 (2, +50 to +58)	-
LV body - Right side	+47 (2, +33 to +61)	+72 (2, +68 to +75)	-
Frontal horn - Left	+15 (3, -8.5 to +35)	-	-
Frontal horn - Right	+2.5 (3, +2 to +24)	-	-
Temporal horn - Left	+18 (3, +2 to +21)	+15 (7, -7.5 to +200)	+17 (3, +10 to +32)
Temporal horn - Right	+13 (3, -1 to +14)	+11 (7, +2.5 to +74)	+9 (3, +5 to +11)
Occipital horn - Left	+31 (2, +30 to +32)	-	-
Occipital horn - Right	+28 (2, +14 to +41)	-	-
Third Ventricle	+19 (5, +6 to +44)	+21 (7, -5 to +52)	+5 (3, 0 to +12)
Pre-frontal lobe - Left	-3.5 (5, -7.5 to +2.5)	-8.5 (2, -15 to -2)	-
Pre-frontal lobe - Right	-1.5 (5, -10.5 to +2)	-7.5 (2, -9.5 to -5.5)	-
Temporal lobe - Left	-6 (5, -13 to +2.5)	-2.25 (4, -5 to +3.5)	+2 (3, -4.5 to +5)
Temporal lobe - Right	-9.5 (5, -15 to +3.5)	-3.75 (4, -9 to +0.5)	-2 (3, -3.5 to +5)
Amyg. & Hipp. - Left	-6.75 (4, -12 to +2.5)	-6.75 (4, -11 to +0.5)	+3.75 (2, +2 to +4.5)
Amyg. & Hipp. - Right	-5.5 (4, -15 to +2.5)	-7.75 (4, -12 to +1.5)	+0.5 (2, -1 to +2)
Amygdala - Left	-	-10 (5, -19 to +15)	-
Amygdala - Right	-	-10.5 (4, -20 to -7)	-
Hippocampus - Left	-	-7 (6, -20 to +1)	-3.25 (2, -7.5 to +1)
Hippocampus - Right	-	-8.5 (6, -15 to -1.5)	-2.5 (2, -12 to +7)
Parahippocampus - Left	-	-14 (3, -15 to -4.5)	-
Parahippocampus - Right	-	-9 (3, -1 to -10)	-
STG - Left	-	-1.25 (4, -7.5 to +1.5)	-7.25 (2, -9 to -5.5)
STG - Right	-	-2.25 (4, -5 to +2.5)	-5.75 (2, -6 to -5.5)

Note: Figures are only given where at least two comparable studies in a subject group are available.

(xiv) Static or progressive ?

A small number of studies have examined first episode patients and suggest that most of the brain changes described in the literature are found at illness onset. Bogerts *et al.* (1990) reported substantial reductions in the temporal lobes and its' component parts, as did Bilder *et al.* (1994). Nopoulos *et al.* (1995) found that the reductions were most marked in the frontal lobes but that these were overshadowed by large increases in total (26%), sulcal (26%) and ventricular (22%) CSF volumes. Without greater certainty about the degree of abnormality found in chronic patients, it is not possible to state whether these changes are entirely developmental, but is safe to say that at least a large part of the structural differences between groups of patients with schizophrenia and normal controls predate the development of florid psychotic symptoms. A more definitive answer could be expected from prospective follow-up studies of patients cohorts.

This issue has been most systematically addressed DeLisi and colleagues at Stony Brook in New York. They first examined a group of 30 first episode 'schizophrenia-like' patients and 15 chronic schizophrenics, and reported significantly larger lateral ventricles (20-44%) in both groups (DeLisi *et al.*, 1991). These differences were generally greater in the chronic patients, and the temporal lobe volumes correlated with duration but not age at onset - suggesting some progression - although ventricular and temporal horn volumes were correlated with age at onset and outcome, but not duration. However, selection of particularly bad outcome patients and a relationship with pre-morbid functioning are alternative explanations (DeLisi *et al.*, 1991). In 24 of these patients who were followed up after two years, non-significant decreases in male and increases in female ventricular volumes were reported and these inversely correlated with symptoms and hospitalisation time - with a greater variance in the volumes in patients (DeLisi *et al..*, 1992). At four years, 20 (15 male) of the original sample were shown to have significantly reduced volumes of both cerebral hemispheres (of about 7cc/year), with a lesser but significant increase of about 1cc per year in the lateral ventricles (left>right). Although

suggestive of true cortical atrophy, interpretation is hindered by the decreasing group sizes (only 5 controls), frequent substance abuse in (at least) 6 patients, and diagnostic changes to schizoaffective disorder in eight cases. No significant deterioration in cognitive functioning was found, but 'left hemisphere function' improvement was strongly and negatively correlated with the reduction in hemisphere volumes (DeLisi *et al.*, 1994)

Although such methodological limitations prevent a definite conclusion, these results do suggest that there is a neurodegenerative component to schizophrenia. The main problem is whether current methods are sufficiently sensitive to detect what is at most a very small difference over and above the inaccuracy of the volumetric technique. For example, Chakos *et al.* (1994) found that cortical volume actually increased, although the ventricular volume decreased, over eighteen months in first episode patients. Clearly, any further cohort studies will need to be conducted on large patient populations. In the meantime, however, some insights into the pathophysiology of schizophrenia can be gleaned from the pattern of correlations between clinical features and MRI regional volumes (and areas).

1.2.3.5 - Correlations of MRI regional areas and volumes

It should be stated at the outset of attempting to review the literature on the associations of brain indices in schizophrenia that it is fraught with dangers of misinterpretation. In particular, the generally small sample sizes of most studies increases the likelihood of Type II errors, while selectivity in reporting of significant correlations (publication bias) is a distinct possibility. Moreover, patients who can consent to and co-operate with scanning procedures may not reflect the generality of all sufferers. Nevertheless, some useful information is available, particularly about the associations with age at onset, outcome, duration and symptom profiles.

(i) Clinical correlations

Area studies have provided conflicting results, with significant correlations reported between brain and cranium areas and negative symptoms (Andreasen *et al.*, 1986); the cerebellar vermis and drug response, and frontal:brain area ratio and negative symptoms (Uematsu & Kaiya, 1988b); the lateral ventricles and poor social outcome (Johnstone *et al.*, 1989b); and between the VBR and positive symptoms, or a small caudate nucleus (and right hippocampus) and more symptoms in general (Young *et al.*, 1991). Andreasen *et al.* (1990) reported that both the VBR and (partial) ventricular volume were related to negative symptoms (and ECT treatment).

Subsequent volumetric studies have failed to find evidence for relationships between brain measures and treatment with either ECT or duration of neuroleptic treatment (Harvey *et al.*, 1993). Indeed, no study has reported a significant correlation between cortical reductions or ventricular increases and antipsychotic medication exposure, and only one has found an association between poor pre-morbid adjustment and any regional volume - the (anterior) cerebral volume, although this was not related to outcome (Harvey *et al.*, 1993). Age at onset has been linked to sulcal:CSF ratio (Mozley *et al.*, 1994), but not to any regional volumes (Zipursky *et al.*, 1994) in individual studies.

Arguably the most consistent correlational finding is the lack of an association between brain parameters and the duration of illness (Kelsoe *et al.*, 1988; Young *et al.*, 1991; Kawasaki *et al.*, 1993; Gur *et al.*, 1994; Zipursky *et al.*, 1994), especially if controlling for age related changes (O'Callaghan *et al.*, 1992; Marsh *et al.*, 1994), although one study did find that duration and total CSF volume were related with or without controlling for age (Gur *et al.*, 1991). There has also been a failure to find regional volume associations with duration in first episode patients (Bilder *et al.*, 1994).

The severity of negative symptoms has been significantly correlated with the volume of the temporal horns of the lateral ventricle (Degreef *et al.*, 1992; Kawaski *et al.*, 1993); the left temporal lobe parenchymal and CSF volumes (Turetsky *et al.*, 1995); cortical grey matter deficits, particularly in frontal regions (Zipursky *et al.*, 1992); and frontal lobe white matter on the left side (Wible *et al.*, 1995). The severity of positive symptoms has been related to the volumes of mesiotemporal structures (Bogerts *et al.*, 1993) and the temporal horns (Degreef *et al.*, 1992), although more studies have not found significant correlations with the volumes of the temporal lobes (Zipursky *et al.*, 1994; Turetsky *et al.*, 1995), the temporal horns (Kawasaki *et al.*, 1993) or the frontal lobes (Wible *et al.*, 1995). Two studies have reported an association between global symptom severity and the volume of the third ventricle (Degreef *et al.*, 1992; Zipursky *et al.*, 1994).

Studies of the links between STG volume and psychopathology have probably provided the best evidence of structural-clinical associations. The first report described a strong correlation (r=+0.7) between left anterior STG deficits and the severity of auditory hallucinations (Barta *et al.*, 1990). However, this result has only been replicated once - for total left STG volume (Flaum *et al.*, 1995), two reports specifically mention finding no association (DeLisi *et al.*, 1994b; Zipursky *et al.*, 1994), and another study found a correlation with the volume of the left anterior cingulate gyrus (Noga *et al.*, 1995). The (left posterior grey) STG has also been linked with thought disorder (r=-0.8, Shenton *et*

al., 1992), although the Harvard group had previously described an association with asymmetrical lateral ventricle volume (Shenton *et al.*, 1991). Zipursky *et al.* (1994) failed to replicate this result, but further studies have reported an intriguing pattern of volumetric-clinical associations. Menon *et al.* (1995), reporting on an extended sample from Barta's study, found a trend to a correlation between grey matter percent of the left mid-portion of the STG and thought disorder, which was very strong if outliers were excluded - although they also found a counter-intuitive association between larger left posterior STG grey matter and higher delusion scores. The Milan group (Vita *et al.*, 1995) have reported significant correlations between the volumes of the left and right posterior STG and incoherence of speech and 'loss of goal' respectively, as well as between abnormal STG asymmetry and thought disorder, although correlations were also found between pre-frontal lobe volumes and various speech and language disorders. A reduction in PT asymmetry has been found to correlate with thought disorder in two studies (Rossi *et al.*, 1994; Petty *et al.*, 1995) but not in two others (DeLisi *et al.*, 1994b; Kleinschmidt *et al.*, 1994).

An alternative approach to the search for clinical relationships is to examine symptom clusters or factors rather than individual features. For example, workers in Philadelphia did not find any individual symptom-volume correlation, but did report that a higher left hemisphere sulcal CSF volume, relative to the right, was associated with factor of negative symptoms, and that increased ventricular:sulcal CSF was correlated with a positive symptoms factor (Mozley *et al.*, 1994). Wright *et al.*. (1995), in London, have developed functional imaging methods for application to segmented structural scans and reported that 'reality distortion' (hallucinations and delusions) was negatively correlated with the grey matter volume in the STG, and that 'psychomotor poverty' (negative symptoms) was associated with increased volume of grey and white matter in left temporal regions, in male patients. Finally, results from the Philadelphia group have recently suggested that MRI-clinical correlational patterns may differ between the sexes e.g. with

increased frontal lobe volume being associated with less disorganisation in men but greater disorganisation and suspiciousness in women (Cowell *et al.*, 1996).

It is difficult to pull this disparate literature together, but it does appear that the regional volume differences between patients with schizophrenia and normal controls are not related to duration of illness or medication, that negative symptoms may be related to cortical loss in the frontal lobes, and that positive symptoms are associated with deficits in parts of the temporal lobes. Although a degree of consensus is evident from these reports, there is more convincing evidence - as with CT - that MRI regional volumes are associated with biological rather than clinical features.

(ii) Correlations with neuropsychological testing and other biological variables

Cognitive deficits in patients with schizophrenia have been found to be significantly correlated with the areas of the cranium/cerebrum (DeMyer *et al.*, 1988; Andreasen *et al.*, 1990), the temporal lobe (DiMichele *et al.*, 1992) and the frontal lobe in one study (Seidman *et al.*, 1994) but not another (Raine *et al.*, 1992). More reliably, the volumes of temporal lobe structures have been linked to language deficits. DeLisi *et al.* (1991) found that verbal memory task performance was inversely correlated with parahippocampal gyrus volumes, particularly in first episode patients. The Harvard group also reported strong associations between the same tests of verbal memory, abstraction and categorisation with the parahippocampal and posterior superior temporal gyrus volumes bilaterally (Nestor *et al.*, 1993). Although the results from the Wechsler Memory Scale did not correlate with temporal lobe or frontal lobe volumes in another study (Seidman *et al.*, 1994), this argues more against crude neuropsychological localisation than against the previous results, and these workers subsequently found a relationship between contextual word recall and frontal lobe volumes (Maher *et al.*, 1995). Vita *et al.* (1995) reported that the left and right posterior STG volumes were related to verbal fluency and object naming, while the total ventricular volume was correlated with sentence generation complexity.

The importance of examining small cortical regions that are associated with discrete cognitive functions was re-inforced by Sullivan *et al.* (1996) when they reported that lower scores on tests of executive function, short term and declarative memory, and motor ability (individual and composite scores) were correlated with smaller total cortical grey matter volume but not with broadly defined cortical regional volumes. Further, the finding that hippocampal abnormalities are related to worse performance on tests usually considered to be sensitive to the integrity of the frontal lobes (Bilder *et al.*, 1994) suggests that integrated fronto-temporal function is disrupted in schizophrenia. Finally, patients with prominent negative symptoms may perform particularly poorly on such frontal lobe tests (Buchanan *et al.*, 1994).

A number of research groups have also related MRI volumes to other biological measures of brain function, such as the event-related potentials and cerebral blood flow or metabolism. Blackwood *et al.* (1991) reported that increased P300 latency was inversely correlated with the area of left and right anterior cingulate cortex, while other groups have found that P3 amplitude reductions are associated with left temporal lobe and right hippocampal areas as well as with positive symptoms (Egan *et al.*, 1994), and volume deficits in the left posterior STG and thought disorder - albeit in one-tailed significance tests (McCarley *et al.*, 1993). In an early attempt to relate structural volume to metabolism, Guenther *et al.* (1989) suggested that reduced callosal area was associated with less motor activation on PET. A series of studies from NIMH have produced results of greater relevance to our current knowledge of schizophrenia and are a model for integration of various findings. Having established that the hippocampus was smaller in the affected twin of discordant pairs (Suddath *et al.*, 1990), they went on to describe that this deficit was associated with a failure to activate the pre-frontal cortex during the WCST (Weinberger *et al.*, 1992) and that the degree of activation was correlated with perseveration errors while the hippocampal volume reduction correlated with verbal memory performance (Goldberg *et al.*, 1994). This work is in keeping with their previous

findings of a correlation between the VBR on CT and prefrontal activation during the WCST, controlling for global blood flow (Berman *et al.*, 1987). Although this has not been exactly replicated (Ford *et al.*, 1992), other groups have found an association between enlarged ventricles and fissures on CT and lower global metabolism (Kling *et al.*, 1986) and between frontal sulcal prominence on CT and reduced resting normalised pre-frontal blood flow (Rubin *et al.*, 1994). These suggestions of abnormal fronto-temporal connectivity are supported by studies of the inter-correlations of structure volumes.

(iii) Inter-correlations of structure volumes on MRI

The total ventricular volume has been found to correlate with cerebral volume (Kelsoe *et al.*, 1988), the temporal lobes and hippocampi - corrected for frontal volume (Suddath *et al.*, 1989), and temporal horn volumes (Kawasaki *et al.*, 1993). However, the correlations are generally weak, some studies have not found such significant correlations (e.g. Bogerts *et al.*, 1990), and ventricular or cerebral volume may not be a true reflection of a loss of brain substance in superficial gyri.

Studies of the relationship between the volumes of the frontal and temporal lobes have also produced interesting results. Correlations have been reported between the right prefrontal white matter and the amygdala-hippocampal complex, the pattern of which were significantly different from controls (Breier *et al.*, 1992); echoing the results from the NIMH reports in discordant twin pairs. Wible *et al.* (1995) also reported a pattern of regional inter-correlations within and between the left anterior temporal lobes and prefrontal lobes, that was not so evident in controls. These results suggest an abnormal excess of fronto-temporal communication, possibly associated with an increase in white matter, that could be responsible for the pathognomic features of schizophrenia.

1.2.4 CONCLUSIONS

The methodological difficulties encountered in studying the cerebral morphometry of schizophrenia are evident from this review. Studies have suffered from small sample size, varying slice thicknesses and boundary definitions; while non-systematic reviews have placed undue emphasis on statistical significance rather than effect sizes (Chua & McKenna, 1994). Nonetheless, methodological variation across studies appear to have had relatively little influence on the main results - with the possible exception of the differences between automated and serial slice measures of the CSF and frontal lobes. Although studies covering only a few slices of the temporal lobes tend to find more significant results than those of the whole lobe, this is probably attributable to greater volume reductions in schizophrenia in anterior temporal lobe structures, and the differences in matched variables or the exact posterior boundary does not seem to be crucial. More evident is the contrasting findings of different groups, for example the greater reductions in frontal lobes in patients in Iowa and the enlarged craniums in males studied in Harvard.

It is clear from the foregoing quantitative review (see Table 1.5) that the brains of patients with schizophrenia (as a group) are generally smaller than those of normal controls, with more specific regional reductions in the temporal lobes and some of its component parts and that the case-control percentage differences are most marked in measures of the ventricular system. It is reassuring to note that these findings are very much in keeping with those from post-mortem studies (Bogerts *et al.*, 1985; Brown *et al.*, 1986; Shapiro *et al.*, 1993), which also agree with the suggestion from this study that the parahippocampal gyrus may be particularly affected. Moreoever, such abnormalities are - at the very least - not so marked in other psychiatric disorders such as manic-depressive psychosis (Johnstone *et al.*, 1989b; Rossi *et al.*, 1991; Harvey *et al.*, 1994; Schlaepfer *et al.*, 1994). However, this review used the medians of percentage differences and therefore does not take account of subject numbers or measurement variance and can not therefore

determine whether the differences described are statistically significant. On the other hand, this approach has the benefit of ease, comprehensibility, and is easily updated to incorporate further studies. It is also possible to say what number of unpublished reports or studies with alternative findings would reverse the apparent consensus, although this is somewhat disquieting e.g. taking the results for the left amygdala in men - only three studies finding no (0%) difference would reduce the median difference to zero. In addition, this review method highlights suitable avenues for further research, such as more thorough examination of the total head size (which may even be increased in men) and altogether more studies in female patients - preferably using comparable methods to the majority of previously published work so that, in time, a more thorough meta-analysis would be a practical proposition. Further systematic work is also required on cerebral asymmetry, changes over time and clinical correlations. Although studies that find a lateralised difference in schizophrenia tend to do so on the left, there is little evidence from the median figures of such leftward laterality except for the ventricular system. The available data are most compatible with the present consensus that these changes are developmental and non-progressive. It is therefore not particularly surprising that studies attempting to relate volume reductions to clinical (state) features have produced inconsistent findings, given that the former may only reflect risk factors for the development of psychosis. In contrast, the relatively consistent associations with cognitive deficits may reflect that these are trait markers.

The next generation of MRI studies in schizophrenia should therefore concentrate on specific populations (such as populations at high risk of developing psychosis), long term follow-up and try to relate abnormalities to stable characteristics such as genetic endowment. There is plenty of room for methodological refinement, as most ably demonstrated by workers at NIMH (Kulynych *et al.*, 1995 & 1996). Larger samples are required, with more females, appropriately matched for age and laterality related variables such as sex and handedness. If asymmetry is to be reliably addressed, any tilt should be

corrected and volume raters should be blind to side (as well as diagnosis). Further technical and methodological improvements will complement the functional capabilities of MRI (see Chapter 4) and those of conventional functional imaging methods, which will now be reviewed.

1.3 FUNCTIONAL BRAIN IMAGING

The demonstration of structural brain abnormalities in schizophrenia adds weight to arguments that it is a disease of the central nervous system, but has only provided limited information as to its nature. Greater insights into such a relatively subtle disturbance have been justifiably expected, and to a certain extent realised, from the examination of functional indices such as cerebral perfusion and neuronal metabolism. Seymour Kety and colleagues (1948) were the first to demonstrate putative 'metabolic derangements' of the brain in schizophrenia and a feasible method of examination. They used invasive measures with nitrous oxide (Kety & Schmidt, 1948), as a diffusible inert index of arterial and venous blood flow (brain uptake being the difference between the two), but could only examine global cerebral blood flow and oxygen consumption and did not find any differences between acute or chronic schizophrenics and normal controls. Many years were to pass before technological advances allowed a greater exploitation of the potential of functional imaging in psychiatric disorders.

Such developments have lead to the two main techniques employed thus far: Single Photon Emission (Computed) Tomography (SPE(C)T) and Positron Emission Tomography (PET). SPET acquires functional (brain) images by detecting the single photons emitted by an administered radio-isotope, while PET is sensitive to the two positrons emitted by annihilation reactions. Although slightly different, both methods depend upon the fact that administered tracers are distributed with regional cerebral blood flow (rCBF) to active areas of the brain, and that such blood flow is tightly coupled to brain metabolism (activity) by autoregulation in physiological and most pathological conditions (Raichle *et al.*, 1976). This introductory review will now briefly describe, in turn, these techniques and their associated problems, before a traditional narrative style summary of the main studies that have been conducted to date. Other functional imaging techniques, including the Electroencephalogram, and evoked potentials, will be briefly discussed in Chapter 4.

1.3.1 SINGLE PHOTON EMISSION TOMOGRAPHY - METHODOLOGY

Measurements of regional cerebral blood flow with collimators were first conducted with radioactive Krypton, although this necessitated surgical brain exposure and was soon replaced by the detection of Xenon (Xe) emitted gamma rays through the intact skull (Glass & Harper, 1963). Improvements in scintillator detection probe sensitivity and curve-fitting algorithms led to the possible use of inhaled or intravenous rather than intra-arterial tracers. Almost co-temporaneously, methods for deriving three-dimensional information form two-dimensional data (tomography) were being devised. SPET systems were soon developed that could determine either the distribution of statistically distributed radiotracers, such as I^{123} labelled compounds, or quantitative measures of dynamic radio-pharmaceuticals such as Xe^{133} (Devous, 1989).

In a SPET scanning session. subjects are first acclimatised to the imaging suite, comfortably placed alongside or in the detector (gamma camera and collimator), given the tracer substance with minimal environmental stimulation (sometimes with ears and eyes patched) and asked to remain inactive during the equilibration period. With the original tracer substance, IMP (I^{123} labelled n-isopropyl p-iodoamphetamine), equilibration of the 3-5mCi (111-185 MBq) dose took 20 minutes, but this is no longer commercially available (Van Heertum & Tikofsky, 1995). With the currently most widely used tracer, 10-20 mCi (370-740 MBq) of ^{99m}Tc-HMPAO (Technetium-hexamethylpropyleneamineoxime / Exametazime) only 5 minutes is necessary for equilibration. The subjects' head is positioned with reference to the orbito-meatal line (OML) to ensure that images are acquired in a comparable way between subjects. During image acquisition, the subjects' head is relatively immobilised, for example with a radiolucent head-holder and zygomatic arch pressure pads, to avoid image degradation.

Early studies used a single detector that spun around the head, within a radius of 14cm, such as a cut-off detector head, long-bore fan beam collimation, or in frontal tomography (Van Heertum & Tikofsky, 1989). Current machines use rotating gamma

cameras, which offer an enhanced image resolution of as low as 10mm, or multiple detector scanners with a resolution of 8-14mm depending on the number of detectors (Kouris *et al.*, 1991). Gamma cameras, also known as scintillation or Anger cameras, are composed of a collimator and a crystal. The origin of the single gamma rays emitted by the radiotracer is calculated from their trajectory through parallel holes in a lead collimator. Gamma rays scintillate on contact with a sodium iodide crystal, the photons then being concentrated by photomultiplier tubes and projected as a two-dimensional image. In general, 64-128 projection times over 30-40 minutes are necessary to acquire images that can be three-dimensionally reconstructed.

Detection systems (large bore collimators) for dynamic or diffusible tracers such as Xe^{133} are sensitive and acquire the images very quickly, with a complete set of projections every 10 seconds (sometimes called dynamic or D-SPECT), but suffer from relatively poor resolution and give a limited number of brain slices as a consequence. Nonetheless, as long as tracer input is measured, e.g. by scintillation over the lungs, absolute quantitative rCBF values (in ml/min/100g brain tissue) can be generated. Static or fixed-tracer tomography, with tracers such as IMP or HMPAO, is less sensitive and takes longer to image the whole brain but has greater resolution. Rotating or multi-detector gamma camera systems can generate contiguous brain sections and have the ability to vary the number of slices and their orientation. Multiple detectors improve energy sensitivity and resolution, but require servicing to ensure that the detectors are aligned linearly and are uniform in sensitivity and can not be used for dynamic imaging, whereas most rotating detector systems can be used for both Xe^{123} and HMPAO scanning as long as different collimators are available (Van Heertum & Tikofsky, 1995).

Radiopharmaceuticals for SPET scanning are of four main types. Firstly, *diffusible* indicators, such as inhaled Xe^{133} (10mCi/minute), which are cheap, give absolute or quantitative data and allow fast imaging time and 5-10 studies per patient lifetime. However, their low energy (80keV) limits resolution, tends to overestimate high blood

flows (especially in white matter), is insensitive to small activity differences at high perfusion and gives limited grey/white matter distinction. Secondly, *I^{123} labelled lipophilics*, such as IMP, generate high energy gamma rays (159 keV) and enhanced photopeak detection and resolution, but may only accurately reflect rCBF for 60 minutes after injection due to re-distribution and do not give absolute values without arterial monitoring. They perform better at high rCBF than HMPAO but are no longer widely used as iodination requires a cyclotron. Thirdly, *^{99m}Tc labelled lipophilics,* such as HMPAO, are now widely available and extensively used as they have a similar distribution and are less expensive than I^{123} lipophilics. Dosimetry permits the use of 10-20mCi per patient-procedure, which shortens imaging time but only allows three investigations in a lifetime. The main problem with HMPAO is with pronounced back-diffusion in high flow regions, which combined with higher extraction in low flow areas can result in poor contrast (Moretti *et al.*, 1995). Finally, *I^{123} labelled neuroreceptor ligands* - for example, the muscarinic agonist I^{123} Quinuclidinyl-iodobenzilate (Eckelman *et al.*, 1984), I^{123} Iomazenil and I^{123} Iodobenzamide (IBZM) - have only limited availability and are expensive. There is no currently available SPET tracer for metabolism, until a simple method of measuring input is devised, but regional blood volume (rCBV) can be measured (albeit with 99mTc tagged red blood cells and a reference blood sample) and the ratio of rCBF to rCBV is related to the oxygen extraction ratio (OER).

1.3.2 SPET IMAGE ANALYSIS AND POTENTIAL ARTEFACTS

Image quality should be routinely measured at intervals throughout the procedure, by closed loop cine or sinogram display, and positioning checked at regular intervals. The detector photomultiplier tubes must be regularly calibrated, uniformity correction ensured using count density correction maps, and detector head centre of rotation maintained, so that acquisition artefacts such as detector non-uniformity ("ring-images") and rotation errors are avoided. After acquisition and adequacy assessment, such as for any movement artefact, the images are pre- or post-processed with a filtered back-projection technique. Excessive or inadequate filtering will reduce image resolution. The rCBF is not easily determined from pixel values with HMPAO or IMP and pixel sizing is crucial for reconstruction, as the image sections should be at least one pixel-width thick (3-4mm) to avoid distortion. Reconstructed axial sections can then be displayed, which gives qualitative visual images, but further processing is necessary for quantitative analyses. Visual inspection can reliably detect structural lesions, asymmetry, frontal lobe abnormalities and activation effects provided multiple experienced raters are employed. Quantitative rCBF data is usually derived by placing interactive regions of interest (ROI), corresponding to anatomical areas, over the image. These can be automatic, derived from a brain atlas, or drawn manually. ROI analysis proceeds by establishing the total tracer count in that region, which is divided by the number of pixels to give an average pixel tracer count per region - which can then be compared to other regions or the same regions in other subjects.

Such comparisons must be 'normalised' to correct for whole brain or whole slice blood flow. Regional tracer uptake results on SPET are usually normalised to the whole slice (although this may obscure effects in regions contained within that slice) or occipital regions (a good reference area, particularly if activation is controlled for with eye patching); rather than to global uptake (which may not be known and diminishes regional effects) or cerebellar uptake (which is difficult to fit to standard ROI's, can be irregularly

shaped, and may itself be involved in many neuropsychiatric disorders (Steinberg *et al.*, 1995a)). However, as with ratio measures in structural scanning, it may be more reliable to control for global CBF statistically, with an analysis of co-variance, rather than normalise to whole brain or particular slices.

Methodological artefacts may arise as a result of differences in scanning protocol. Even having the eyes open or closed may alter rCBF symmetry and reproducibility, in that the more "physiological" condition of eyes open may give more reproducible results, with less variability, as long as stimulation is minimised (Devous, 1989). Similarly, administration of sedatives or anticholinergics to minimise movement may alter tracer distribution. As with all imaging techniques, resolution and partial volume effects are important considerations.

1.3.3 SPET STUDIES IN NORMAL SUBJECTS

Neurophysiological studies with SPET were dependent on Xe^{133} D-SPECT alone until HMPAO became widely available in the past decade. Even the separate measurement of rCBF in grey (70-90ml/min/100g) and white (20-30ml/min/100g) matter has only been possible since the late 1960's, and methodological artefacts with Xenon methods are a substantial concern. For example, inferior frontal regions can be contaminated by inhaled gas in the nasal passages and cause a false 'hyperfrontality', isotope scatter can lead to a potential overestimation problem - particularly in low flow (white matter) areas - and the later Xe^{133} tomography method gives higher white matter flows of 60ml/min/100g. Nonetheless, there are several replicated reports of functional activations with the Xe inhalation method that are in agreement with results from PET (Devous, 1989; George *et al.*, 1991). For example, attending to tasks or somatosensory stimulation increases frontal blood flow (Devous, 1989), Broca's area is activated during speech and visuospatial problems activate right parieto-occipital regions (Gur *et al.*, 1982), and the Stroop test produces activations of the mesial frontal region (Larrue *et al.*, 1994). Pharmacological activations have also been possible with Acetazolamide, Arecoline and inhaled carbon dioxide (Devous, 1989). Such sensory, cognitive or pharmacological stimulation in SPET (as in PET) produces activations in which the magnitude of blood flow increases with stimulus complexity and rate, and the subjects' attention.

Basic neurophysiological studies with SPET are perhaps of greatest interest to the neuropsychiatrist as they can identify generally important determinants of rCBF that may confound clinical studies. Females have been consistently shown to have increased cerebral perfusion as compared to men, but the studies differ as to whether this is a global effect (Gur *et al.*, 1982) or one that is greatest in frontal regions (Mathew *et al.*, 1986; Daniel *et al.*, 1988). This may even apply to men with high self ratings of femininity (Daniel *et al.*, 1988). Increasing age is associated with reductions in blood flow that are

most marked anteriorly (Gur *et al.*, 1986; Mathew *et al.*, 1986), but cognitive activations - at least to visuospatial tasks - can still provide the expected extent and pattern of rCBF changes (Gur *et al.*, 1986). The extent of cerebral dominance, as measured with the handedness, is associated with rCBF laterality but the effect is small - strong left handers showing a 4% greater degree of the normal right sided increase in rCBF - and blood flow to the hemispheres is highly correlated (Prohovnik *et al.*, 1980). Asymmetry is generally minimal, perhaps with a difference of up to 3ml/min/100g, and generally increased rCBF on the right side (Devous, 1989). Caffeine and nicotine appear to be global vasoconstrictors (Mathew *et al.*, 1983) and vasodilators (Mathew *et al.*, 1986) respectively. Anxiety can both increase and decrease rCBF depending on severity and chronicity (Mathew & Wilson, 1990), while habituation to scan procedures will inevitably reduce perfusion (Prohovnik *et al.*, 1980). Thus, although the Xenon inhalation method may be relatively insensitive, it can nonetheless discriminate between whether the eyes are open or closed during scanning, and is sensitive to the potentially confounding effects of age, sex, handedness, anxiety, attention, time of the day, blood pressure and arterial carbon dioxide levels (Devous, 1989).

The improved resolution with HMPAO might be expected to show even greater effects of such variables, but few studies have examined these issues. Certainly, however, it has been established that SPET with this tracer can reliably detect appropriate cortical activations on sensory (Woods *et al.*, 1991; Crosson *et al.*, 1994), motor (Ebmeier *et al.*, 1992; Crosson *et al.*, 1994), cognitive (Shedlack *et al.*, 1991) and pharmacological (Tiihonen *et al.*, 1994) stimulation. The lack of attention to studies of the determinants of Exametazime measured rCBF in normal controls is disappointing, particularly as most of the SPET studies in schizophrenia over the past five years have used this method. These studies, and those employing Xenon inhalation, will now be reviewed, according to whether they used resting or activated experimental conditions.

1.3.4 SPET STUDIES IN SCHIZOPHRENIA

Functional imaging in schizophrenia research has primarily concentrated on so-called 'hypofrontality'. Such a relative reduction in frontal rCBF was first suggested in a series of studies by workers in Lund, Sweden. Using an intra-carotid injection of Xe^{133} and 32 probes around the left hemisphere, they initially demonstrated that patients with chronic schizophrenia had relatively low blood flow to frontal regions, that post-central flow correlated with 'cognitive disturbance' (thought form and content), and that the most 'autistic' patients showed the least activation on a simple object naming test (Ingvar & Franzen, 1974a). They took these observations forward by showing that symptoms of indifference, inactivity and autism were negatively correlated with frontal flow (Ingvar & Franzen, 1974b), and that hypofrontality persisted in schizophrenic subjects on cognitive activation (Franzen & Ingvar, 1975). As the levels of medication did not correlate with other findings, the authors concluded that there was evidence of defective neuro-transmission in the mediothalamic frontocortical projection bundle in chronic schizophrenia.

1.3.4.1 Xenon inhalation studies

Subsequent Xe^{133} studies have used the less invasive inhalation method, with cortical probes or SPECT, although this has a lower regional resolution. Mathew and colleagues found no hypofrontality, but generalised rCBF reductions in patients with schizophrenia, regardless of whether they were on medication or had been withdrawn for one week, and hallucination severity was inversely correlated with postcentral blood flow (Mathew *et al.*, 1981 & 1982). Ariel *et al.*. (1983) did find reduced grey matter rCBF values in frontal areas bilaterally, although this was only significant in the left hemisphere. No significant reductions in resting rCBF were found by Pennsylvania researchers in either medicated or unmedicated patients (Gur *et al.*, 1983 & 1985), but these experiments were conducted on only 15 and 19 subjects respectively and there is only one other Xe study (also in small numbers) to find no such effect (Dousse *et al.*, 1988). In contrast, hypofrontality at rest was reported in several other early studies in medicated (Mubrin *et al.*, 1982; Kurachi *et al.*, 1985; Mathew *et al.*, 1988) and unmedicated patients (Weinberger *et al.*, 1986; Berman *et al.*, 1986; Geraud *et al.*, 1987), or both (Warkentin *et al.*, 1990). Kurachi *et al.*. (1985) also found a 'hyper-temporality' that was greatest on the left in patients with auditory hallucinations, while Mathew *et al.* (1988) reported left temporal rCBF reductions and that illness duration was related to hypofrontality.

The few resting Xe^{133} D-SPECT studies have also reported hypofrontality in medicated, unmedicated and first episode patients (Paulman *et al.*, 1990; Sagawa *et al.*, 1990; Steinberg *et al.*, 1995b). Moreover, medication effects appear, if anything, to decrease rather than worsen the severity of hypofrontality (Matsuda *et al.*, 1991). Paulman and colleagues (1990) also found that reduced left frontal rCBF was associated with neuropsychological impairment on the Wisconsin Card Sort Test (WCST) and that increased hemispheric blood flow was correlated with positive symptoms.

More consistent differences between patients with schizophrenia and normal controls have been found on various cognitive activations. In Philadelphia, medicated

schizophrenic patients had aberrant hemispheric activation patterns, with left sided rCBF increases on a spatial task and bilateral increases for a verbal task (Gur *et al.*, 1983); a pattern that was not substantially different in unmedicated patients (Gur *et al.*, 1985). In the first of an influential series of studies, workers at NIMH showed that medication-free schizophrenic patients had smaller relative and absolute increases in dorso-lateral pre-frontal cortex (DLPFC) flow than controls while performing a slightly modified version of the WCST, but not during a number-matching task, and that DLPFC rCBF correlated with performance (Weinberger *et al.*, 1986). They confirmed these findings in medicated patients and established that DLPFC rCBF was not reduced on a visual continuous performance test (Berman *et al.*, 1986). This was employed as a baseline reference to reduce resting rCBF variability and suggests that rCBF deficits were not simply attributable to a generally poor performance or lack of attention to the task. Two later studies reported a correlation between monoamine metabolite concentration and activated DLPFC rCBF (Weinberger *et al.*, 1988), and that Raven's Progressive Matrices activations were post-central and no different between cases and controls (Berman *et al.*, 1988). Some support for the WCST related DLPFC deficit has been forthcoming (Sagawa *et al.*, 1990; Steinberg *et al.*, 1996). The NIMH researchers have also refuted evidence of abnormal lateralisation in schizophrenia beyond any task dependent increases in left anterior and right posterior regions (Berman & Weinberger, 1990); and reported WCST related DLPFC deficits in schizophrenics, but not their unaffected co-twins, that were related to hippocampal volume (Berman *et al.*, 1992; Weinberger *et al.*, 1992). Wood and Flowers (1990) reported hypofrontality and reduced activation of language areas on verbal memory tasks in patients as compared to normal controls. Finally, Andreasen *et al.*. (1992) studied never medicated and currently unmedicated patients performing the Tower of London test. Activations were reduced in the left mesial frontal cortex in both groups, particularly in those with negative symptoms, while neither medication nor task performance were significantly associated with rCBF.

1.3.4.2 HMPAO studies

There are fewer studies using HMPAO as the tracer as it has only been widely available for less than ten years. However, the enhanced resolution of grey/white matter and ability to image subcortical structures with HMPAO has brought definite advances, despite the somewhat reduced sensitivity with this technique as compared to Xenon inhalation. The first study failed to detect hypofrontality (Bajc *et al.*, 1989), as have some other small studies (Kawasaki *et al.*, 1992; Rubin *et al.*, 1991 & 1994), but power issues are paramount here as a combined analysis of the Rubin studies did find relative hypofrontality (Rubin *et al.*, 1994). Nonetheless, only a few other studies have detected resting hypofrontality with HMPAO (Erbas *et al.*, 1990; Dupont *et al.*, 1994; Vita *et al.*, 1995) and some have actually reported 'hyperfrontality' in ummedicated patients with acute illness (Ebmeier *et al.*, 1993; Catafau *et al.*, 1994; Parallada *et al.*, 1994).

The main advantage of HMPAO has been in imaging specific anatomical regions and thereby allowing meaningful clinical correlational analyses. Ebmeier *et al.* (1993) found that negative symptoms were associated with resting reduced prefrontal rCBF and that disorganisation was positively correlated with cingulate tracer uptake. Some studies have reported 'hypotemporality' in medicated patients (Catafau *et al.*, 1994; Dupont *et al.*, 1994), but Kawasaki and colleagues (1992) found increases in resting relative left hippocampal and basal ganglia blood flow that were inversely correlated with negative symptoms. This apparent discrepancy may be related to the levels of particular clinical features in different patient groups - in a within-subjects follow-up study McGuire *et al.*. (1993) found that auditory hallucinations were associated with increased blood flow in inferior frontal (Broca's area) and anterior cingulate cortex.

Activation experiments with HMPAO-SPECT have at least confirmed earlier reports of hypofrontality. Lewis *et al.*. (1992) found reduced lateral and medial frontal perfusion on a word fluency test, with negative symptoms being correlated with mesial blood flow and performance with lateral rCBF. A failure of (usually left sided) lateral and

medial pre-frontal cortex activation with the WCST has been replicated in unmedicated and neuroleptic-naive subjects (Rubin *et al.*, 1991 & 1994; Kawasaki *et al.*, 1993; Paralleda *et al.*, 1994; Catafau *et al.*, 1994). Workers at the Institute of Psychiatry have tried to shed light on medial temporal lobe functioning in schizophrenia with verbal memory testing. The first study identified generally greater rCBF increases in the left medial temporal and anterior cingulate cortices (Busatto *et al.*, 1994), while the second showed left basal ganglia hyperactivity in hallucinating patients that was not related to medication levels (Busatto *et al.*, 1995). A previous resting study found a similar association between hallucinations and subcortical blood flow (Musalek *et al.*, 1989), as has another in which a failure of striatal suppression was evident during the WCST in never medicated patients (Rubin *et al.*, 1991). Such a failure to deactivate the left striatum might conceivably be related to postulated internal monitoring deficits in schizophrenia.

1.3.4.3 Other SPET studies

There are a handful of SPET reports using the tracer IMP or the dopamine ligand IBZM in patients with schizophrenia. Resting IMP studies have shown both hypofrontality (Suga *et al.*, 1994) and hypotemporality (Cohen *et al.*, 1989a), while two reports have described increased IMP uptake in left superior temporal regions during active hallucinating (Matsuda *et al.*, 1989; Suzuki *et al.*, 1993) and factor analysis has related negative symptoms to hypofrontality, disorganisation to the anterior cingulate cortex and hallucinations to right sided rCBF increases (Yuasa *et al.*, 1995).

IBZM is a highly specific D2-receptor ligand with relatively specific striatal uptake and a long radioactive half-life, making it suitable for in vivo ligand studies. Pilowsky and colleagues compared IBZM binding in patients on standard and atypical neuroleptics and found that therapeutic response was not dependent upon D2 blockade (1992); and went on to establish that there was no difference in striatal D2 receptor availability in typical antipsychotic responders and non-responders (1993). Other researchers have largely confirmed these findings (Volk *et al.*, 1994; Klemm *et al.*, 1996), while Sherer *et al.*. (1994) found that striatal receptor occupancy was related to extra-pyramidal side effects. These studies not only challenge the simple dopamine model of schizophrenia, but also suggest that such techniques could improve drug monitoring in clinical practice.

1.3.5 CONCLUSIONS FROM SPET STUDIES IN SCHIZOPHRENIA

It is apparent that an 'absolute' hypofrontality, as measured with Xenon inhalation, is a relatively robust finding in the studies of schizophrenia and that it does not appear to be an artefact of medication exposure. The results are much less consistent with the tracer HMPAO, but the enhanced spatial resolution it affords will allow the detection of more specific areas of increased and decreased rCBF in further studies. Activation experiments with both techniques reliably show hypofrontality - particularly with the WCST - which is, if anything, improved with treatment. Although such impairment could simply reflect a worse performance on the task, it can be seen that frontal lobe function is disturbed in schizophrenia. The majority of clinical correlation studies show that such frontal rCBF deficits are related to negative symptoms, while acute episodes tend to be associated with increases in frontal perfusion. Auditory hallucinations appear to result from a dysregulated neuronal circuit that includes cingulate, temporal and subcortical regions; and whether perfusion is increased or decreased may depend on methodological factors such as the reference region. However, few of these findings appear to be specific to schizophrenia. Similar abnormalities, of general hypoperfusion (Mathew *et al.*, 1980), rCBF asymmetry (Gur *et al.*, 1984), hypofrontality (Austin *et al.*, 1992) and hypertemporality (Zohar *et al.*, 1989), have been reported in the affective disorders. Berman *et al.* (1993) reported that WCST activated hypofrontality was not found in depression, but they only included ten patients in the study. Future research should concentrate on using larger samples of patients, novel activation paradigms, and determine whether hypofrontality is attributable to structural tissue loss.

SPET does suffer from poorer resolution, worse (Compton) scatter and a greater need for attenuation correction than PET, which can also give absolute values of rCBF or substrate use and neuroreceptor density or occupancy. Ironically, however, improvements in SPET technology have been hindered by the amount of attention given to PET scanning (Rosenthal *et al.*, 1995).

1.4 POSITRON EMISSION TOMOGRAPHY (PET)

1.4.1 PET METHODOLOGY

PET is most commonly employed to measure the regional cerebral metabolic rate in terms of glucose utilisation (rCMRgl). The PET scanner uses a ring of radiation detectors to produce images of the distribution of radio-isotopes in the brain. The isotopes are labelled with one of four radionuclides - ^{11}C, ^{13}N, ^{15}O, and ^{18}F - which are unstable, have an excess of protons and emit positrons during radioactive decay. The positrons travel a certain distance (1-3mm) before losing kinetic energy and colliding with a free electron, with the consequent emission of two 511 KeV gamma ray photons at 180 degrees to each other (Buchsbaum, 1987). (From the laws of energy and momentum conservation, and $E = mc^2$, 511KeV is the energy equivalent of the mass of a positron).

Gamma-sensitive radiation detectors, usually of either sodium iodide or bismuth germinate crystals, scintillate in response to two simultaneous (within 5-20 nanoseconds) photons at 180 degrees in a 'coincidence circuit'. The brain image is reconstructed from a filtered-back projection algorithm of all these coincidence lines, with filtering ('smoothing') chosen to balance propitious spatial resolution against statistical noise and edge effects. Basic positron physics - the distance travelled ('positron range'), the difference in arrival time ('time of flight'), and any momentum at collision leading to angular deviation from 180 degrees ('non-colinearity') - limit the ultimate resolution of PET to 2-3mm, although technical developments could improve on the current resolutions of 5-10 mm (Buchsbaum, 1987).

For quantitative analyses the photon count must be converted into true radioactivity, with corrections for attenuation (as a result of photon energy loss or the scattering by brain tissue, which is most marked in central tissues), finite resolution (blurring of large structures), partial volume effects (underestimation of counts in small structures due to dilution from surrounding tissue), random coincidences and the inevitable statistical noise from radioactive decay. By comparison with the substrate

concentration in the blood, together with a mathematical model of metabolism, the metabolic rate of each element of the brain image is calculated (Holcomb *et al.*, 1989). PET measurements of metabolism depend on the observation that the functional capacity of the adult brain is almost entirely dependent on oxidative glucose consumption, although the usual tight coupling between rCBF and oxygen extraction is loosened in some acute diseases and on acute physiological stimulation (Raichle *et al.*, 1976; Fox & Raichle, 1986; Fox *et al.*, 1988).

Particular nuclides are incorporated into specific compounds for use in different techniques for determining metabolism. The rate of utilisation of ^{15}O-labelled carbon monoxide/oxygen/water are examples, but the half-life of only two minutes dictates that steady state activity is more accurately measured than physiological changes in activity. The latter requires a longer nuclide decay, to allow a sensitive and robust detection of physiological processes, such as the fifteen minute half-life of ^{11}C-labelled 2-deoxy-D-glucose (2DG). 2DG is used rather than labelled glucose as it accumulates (for at least 40 minutes) as 2DG-6-phosphate after metabolism by hexokinase, rather than progressing further along the glycolytic pathway, and is only slowly metabolised by phosphatase or removed from the cell thereafter (Phelps *et al.*, 1981a; Nelson *et al.*, 1986). The most commonly used nuclide is ^{18}F-labelled 2DG (FDG) as this has a half-life of 110 minutes, allowing multiple scans and sequential activations in the same session, with the possibility of delineating specific functional anatomy in adjacent brain areas by appropriate subtractions from baseline activity - which would otherwise demand multiple radio-isotope dosing (Fox *et al.*, 1986).

PET can also be employed to determine neurotransmitter turnover, by administering a radioactive substrate (e.g. ^{18}F-L-dopa), and receptor quantification by a variety of techniques involving labelled ligands. In vivo receptor density measurement, which is the more relevant technique to psychiatric research, can be undertaken by either single-dose tracer kinetics or saturation analysis at equilibrium (Wagner *et al.*, 1983;

Sedvall *et al.*, 1986). A ligand's retention by a receptor population (binding potential) is the product of its tendency to dissociate from binding sites at equilibrium (Kd) and the number of sites available (Bmax). Tracer activity in the caudate-putamen is curvilinear and taken as a measure of total binding (especially if receptor numbers are low), whereas that in the cerebellum is linear and reflects non-specific and free binding, the difference between the two being specifically bound ligand (Wagner *et al.*, 1983). Such calculations can be facilitated (increasing signal to noise) by comparing the binding before and after the administration of an unlabelled ligand such as haloperidol, which lowers the available number of receptors. Kinetic studies use ^{11}C-3N-methylspiperone (NMSP) or one of its analogues as the tracer, which are assumed to bind irreversibly and only require one pre-treatment. Saturation experiments use ^{11}C-raclopride and assume that brain tracer metabolism is minimal, equilibrium is quickly attained, and that endogenous dopamine and non-specific binding are negligible; as such, the cerebellar concentration essentially reflects only free ligand, but this method requires larger doses of radioactivity due to sequential imaging with different amounts of unlabelled raclopride (Sedvall *et al.*, 1986). These techniques can also be employed to estimate the receptor occupancy of different medications as used in clinical practice, but all PET techniques are methodologically complex and the results obtained are therefore subject to a number of possible artefacts.

1.4.2 PET METHODOLOGICAL PROBLEMS AND POTENTIAL ARTEFACTS

Provided that the head is immobilised, the most important methodological concern in PET studies is that the inter-subject variability in brain size and shape are controlled for so that comparable functional localisations are possible. Head position must first be standardised, usually by reference to inter-commissural line (the AC-PC plane), before functional-structural image co-registration with CT/MRI or a pixel-by-pixel matching to a standard template in stereotactic space, followed by 'redirected sampling' to allow for measurements of regional brain tissue activity (Bench *et al.*, 1990). Pixel matching must be accurate as misalignment by as little as 3mm can substantially alter the activity detected, especially where grey/white matter differences in isotope concentration can be as high as 100%. This sort of error might also compound, for example, the yield of artificially low grey matter values (of 50-60 ml/100g) with O^{15} water studies.

Unless the scanner covers the whole brain, there will be some 'dead space' where portions of some structures - such as the basal ganglia - are not imaged. Such partial volume effects increase measurement error and are most pronounced in small, thin or wedge-shaped structures than larger spherical ones (Buchsbaum, 1987). The diameter of a circle where the count rate is 50% of that at the centre is the full-width at half-maximum (FWHM) value and approximates to the image resolution. A structure that is only as wide as the FWHM will have a measured value diluted by about 70% (Buchsbaum, 1987), while two activated structures separated by only the FWHM cannot be distinguished from each other unless sequential activations are undertaken (Fox *et al.*, 1986).

Statistical analysis faces the problem of numerous (highly correlated) measurements in a relatively small number of subjects. These problems are reflected in the use of at least seven different analytical strategies in the early PET literature (Holcomb *et al.*, 1989). Further difficulties in comparing studies arise from the lack of standardised physio-behavioural test conditions, the high levels of inter-subject variance that are compounded in studies of heterogeneous disorders, and uncertain inter-relations between

task activations in various patient groups. A within-subject test-retest design therefore has maximal power and reliability; preferably with analysis by principal components structure in the same subjects under multiple conditions.

Workers at the Hammersmith in London have developed more refined analysis techniques than those in early use. Whereas researchers used to employ a region of interest method in individual slices, Friston et al. (1990 & 1992a) have devised a Statistical Parametric Mapping (SPM) programme which allows coverage of the whole brain. Activated areas are identified by a conservative measure of statistical significance, with an analysis of co-variance to control for global blood flow changes and a principal components analysis to examine functional connectivity between discrete areas.

Finally, differences in subject groups are an important possible source of artifactual results. Such subjects are inevitably selected on the basis that they can comply with the immobilisation over a period of time demanded by the procedure. Differences in age, sex distribution, anxiety levels or habitual amounts of drug consumption can systematically confound the results obtained. There is an age related decline in blood flow to grey but not white matter, which is not paralleled by a decline in oxygen metabolism (Bench *et al.*, 1990). While global metabolism may not differ between relatively young age groups, relative frontal metabolism does appear to decrease from an early age (Wang *et al.*, 1994) and dopamine receptor numbers fall by approximately 10% per decade (Wong *et al.*, 1984). Females have greater glucose metabolism in all brain regions than men (an average of 19%) which may vary across the menstrual cycle (Baxter *et al.*, 1987). Finally, both low levels of arousal/anxiety and acute administration of many drugs may increase rCBF and metabolism, while severe anxiety and chronic drug abuse reduces these measures (Mathew & Wilson, 1990 & 1991). The latter findings appear to apply to both normal subjects and those with psychiatric disorders.

1.4.3 PET STUDIES IN NORMAL SUBJECTS

A substantial body of experimental work has been performed with PET in normal subjects, with activation by sensory, cognitive or pharmacological stimulation (Roland, 1993). Visual tasks result in 8% greater glucose use in the contralateral hemisphere with hemi-field stimulation (Greenberg *et al.*, 1981), bilateral increases of up to 50% with a reversing checkerboard (Fox *et al.*, 1986; Fox *et al.*, 1988), and glucose use increases further - by a factor of two - with an increasing complexity of visual stimuli (Phelps *et al.*, 1981a&b). Light stroking of the hand results in 9% greater contralateral metabolic activity (Greenberg *et al.*, 1991), while vibratory somatosensory stimulation focally increases the rCBF in contralateral sensorimotor cortex by as much as 29% (Fox & Raichle, 1986). Auditory stimulation experiments have demonstrated that glucose use increases with attention to the stimulus, and that using an analytic strategy to remember a sequence of tones results in greater left sided metabolism (especially of mesial temporal lobe structures) whereas a non-analytic strategy increases right side use more (Mazziotta, 1985). Further evidence suggests that the hippocampus is particularly important in memory function (Squire *et al.*, 1992), although particular episodic or semantic memory tasks selectively activate additional cortical regions (Paulesu *et al.*, 1993; Shallice *et al.*, 1994). Such experiments are even beginning to shed light on the nature of consciousness itself with, for example, demonstrations that multiple sensory representations of the body exist in the brain that contribute to perception (Bottini *et al.*, 1995) and that both random and focused episodic memory activate medial frontal and limbic regions which may underlie the experience of identity and self-awareness (Andreasen *et al.*, 1995). It should be borne in mind that such insights have been derived from sequential activation and subtraction experiments, whereas the early research in schizophrenia was largely limited to resting studies. This has undoubtedly contributed to increased measurement variance and slowed the delivery of consensus regarding functional imaging findings in schizophrenia.

1.4.4 PET STUDIES IN SCHIZOPHRENIA

1.4.4.1 Resting Studies

The first replicated finding with PET studies in schizophrenia was the demonstration of "hypofrontality" and most subsequent studies have focused on this issue. Buchsbaum and colleagues (1982) at NIMH were the first to demonstrate this, reporting that the relative frontal:occipital FDG-CMRgl (and left central grey matter utilisation) at rest was significantly reduced in 8 unmedicated patients as compared to 6 normal controls. Subsequent resting FDG studies have reported relative (Farkas *et al.*, 1984; DeLisi *et al.*, 1985a) or absolute (Wolkin *et al.*, 1985) reductions in frontal:occipital metabolism, or both (Wolkin *et al.*, 1988; Siegel *et al.*, 1993), and most of those to find neither (Kling *et al.*, 1986; Gur *et al.*, 1987b; Tamminga *et al.*, 1992) have still found non-significant reductions. Although the subjects in these studies have either been medicated or only off medication for about two weeks, medicated and unmedicated patients were no different in one study (Farkas *et al.*, 1984), and prospective studies have found that relative hypofrontality persists after treatment despite a general improvement in glucose utilisation (Farkas *et al.*, 1984; DeLisi *et al.*, 1985b; Wolkin *et al.*, 1985) - although others have found hypofrontality to be compounded in patients with prominent negative symptoms (Buchsbaum *et al.*, 1992; Wolkin *et al.*, 1996). However, Cleghorn's group in Ontario have reported relative hyper-frontality in both medicated (Szechtman *et al.*, 1988) and drug-naive patients with schizophrenia (Cleghorn *et al.*, 1989); and Gur *et al.* (1995) also reported non-significant tendencies to increased frontal metabolism in first episode and medication free patients.

FDG studies have also tended to report some extent of absolute or relatively reduced glucose metabolism in the temporal lobes (Buchsbaum *et al.*, 1982; Wolkin *et al.*, 1985; Gur *et al.*, 1987b; Cohen et al., 1989b; Tamminga *et al.*, 1992; Siegel *et al.*, 1993), although some have found 'hyper-temporality' (DeLisi *et al.*, 1985b&c; Gur *et al.*, 1995) particularly on the left side. The other brain region to receive extensive study, the

basal ganglia, has been shown to have generally reduced absolute metabolism but less consistently reduced relative CMRgl (Buchsbaum *et al.*, 1982; Wolkin *et al.*, 1985; Buchsbaum *et al.*, 1987; Gur *et al.*, 1987b; Resnick *et al.*, 1988; Szechtman *et al.*, 1988; Cohen *et al.*, 1989b; Tamminga *et al.*, 1992; Siegel *et al.*, 1993; Gur *et al.*, 1995). A possible explanation of these inconsistencies is that metabolism is habitually increased in both temporal lobes and the basal ganglia by antipsychotic medication (Wolkin *et al.*, 1985; DeLisi *et al.*, 1985b; Buchsbaum *et al.*, 1987; Holcomb *et al.*, 1996), so that the medication status of patients is particularly important when studying these regions. Other statistically significant results of interest to be reported with FDG-PET include 'hypo-parietality' (Cleghorn *et al.*, 1989), an increased sub-cortical/cortical gradient (Gur *et al.*, 1987b) and greater left-right asymmetry in unmedicated patients (Gur *et al.*, 1987b).

Some of these findings have been replicated by researchers using other radio-isotopes, such as carbon-11 labelled DG, in PET studies of schizophrenia. Volkow et al. reported general hypermetabolism in unmedicated patients that did not alter substantially after treatment (1986), and widespread hypometabolism but hyper-subcorticality in medicated patients (1987). Other 'CDG' findings include hypofrontality and hypoparietality in sub-groups of medicated patients (Kishimoto *et al.*, 1987), and left sided hypofrontality and hypotemporality in unmedicated patients (Wiesel *et al.*, 1987a). Two studies using the oxygen steady-state technique have failed to demonstrate hypofrontality (Sheppard *et al.*, 1983; Early *et al.*, 1987). The former study included medicated patients and found reduced basal ganglia activity and diminished left-right asymmetry, while the latter (in never medicated patients) reported increased left globus pallidus blood flow in never medicated patients. However, as with SPET, more consistent results have been forthcoming in activation experiments.

1.4.4.2 Activation experiments

The main advantage of activated measures of metabolism is that this is a relatively straightforward method of controlling for inter-individual behavioural and physiological differences. The first such study reported that patients with schizophrenia (and bipolar affective disorder) showed a lower anteroposterior gradient and lesser lateralisation than controls after unpleasant electrical stimulation to the right arm. However, this did not necessarily mean reduced metabolism in frontal regions, as an increased posterior utilisation was responsible for the reduced gradient (Buchsbaum *et al.*, 1984). On auditory vigilance tasks, schizophrenics have shown non-significant hypofrontality and significant hypertemporality in one study where only six patients were examined (Jernigan *et al.*, 1985), and significantly reduced metabolism in the middle frontal and anterior temporal lobes in a larger study of drug-free subjects (Cohen *et al.*, 1987). Other FDG activation experiments, employing visual continuous performance tests (CPT), have reported relative hypofrontality, hypotemporality and diminished subcortical metabolism in both ex-medicated (Buchsbaum *et al.*, 1990) and never-medicated patients (Buchsbaum *et al.*, 1992), and in a large series of 83 subjects (Schroeder *et al.*, 1994), although these results have still to be independently replicated. The remaining FDG activated experiment has found evidence of significantly reduced left temporal metabolism on amphetamine challenge, which was associated with negative rather than positive symptoms (Wolkin *et al.*, 1994).

Various researchers have also used other PET techniques to measure activation and some (in the case of the London group) have devised highly innovative cognitive stimulation procedures. Guenther et al. (1994), using carbon-11, reported results suggestive of an abnormal (hypofrontal-hypersubcortical) pattern on motor tasks that was in keeping with their previous study (Guenther *et al.*, 1989). The only other carbon-11 study examined the effects of an eye-tracking task in 18 medicated schizophrenics and revealed marked hypofrontality both at rest and on activation (Volkow *et al.*, 1987).

Nakashima et al. (1994) also found a failure of frontal activation in medicated and unmedicated patients whilst performing visually and memory guided saccades, although $H_2{}^{15}O$-rCBF was actually higher in all conditions in the patients.

Workers at the MRC Cyclotron Unit in London, using the $H_2{}^{15}O$ technique, have particularly focused on the functional anatomy of auditory hallucinations as one of the central features of the disorder. Following their demonstration of increased rCBF in Broca's area during hallucinations (McGuire *et al.*, 1993), they asked hallucinators and non-hallucinators to imagine being spoken to in another person's voice. All groups, including controls, exhibited a normal left frontal response but only the hallucinators had reduced activation in the left middle temporal gyrus and rostral supplementary motor area - suggesting that a predisposition to such phenomena is associated with a failure to activate areas concerned with the monitoring of internal speech (McGuire *et al.*, 1995). In another experiment, with paced verbal fluency that matched for performance, chronic patients showed (if anything) a greater spatial extent of activation in the DLPFC and a convincing lack of rCBF reductions in the left superior temporal cortex as was found in simple word repetition (Frith *et al.*, 1995). These workers have also recently examined the effect of dopaminergic (apomorphine) modulation of the neural response to paced verbal fluency and found that the impaired activation of anterior cingulate was reversed into a significantly augmented response as compared to normal controls (Dolan *et al.*, 1995). These findings not only provide a bridge between the putative neuropharmacological and cognitive abnormalities in schizophrenia, but have also been seen as evidence against simple hypofrontality and for hypotheses of abnormal fronto-temporal connectivity. The latter, in particular, has also been supported by some of the findings from clinical correlational analyses of PET data.

1.4.4.3 Clinical and Biological correlations

Many workers have attempted to relate abnormalities of metabolism to the clinical features of schizophrenia. There are, in particular, strong suggestions that hypofrontality may be related to the presence of negative symptoms (Volkow *et al.*, 1987; Wiesel *et al.*, 1987a; Tamminga *et al.*, 1992; Wolkin *et al.*, 1992; Schroder *et al.*, 1996) or total symptomatology (Siegel *et al.*, 1993). Hypertemporality may be associated with both positive and negative symptoms (Gur *et al.*, 1995; Schroder *et al.*, 1996), but Wiesel *et al.*, (1987a) found the relationship was with reduced temporal metabolism. The severity of hallucinations has been positively correlated with anterior cingulate metabolism and may also be associated with reduced metabolism in the auditory cortex and Broca's area (Cleghorn *et al.*, 1990 & 1992). The London group reported that auditory hallucinations were associated with activation in limbic (hippocampus), paralimbic (parahippocampus) and subcortical (thalamus) structures, as well as the right anterior cingulate, and also found that the association cortices were activated in a single case with both visual and auditory hallucinations (Silbersweig *et al.*, 1996).

Following the lead of Liddle et al. (1992), other groups have shown a negative symptoms factor ('psychomotor poverty') to be related to left DLPFC metabolism, positive symptoms ('reality distortion') with right medial prefrontal cortex (and left temporal) metabolism, and disorganisation with left superior temporal activity (Kaplan *et al.*, 1993; Schroder *et al.*, 1996). Although the sign of these correlations, and their precise location, differs in some of these studies this could be attributable to whether the patients are fundamentally hypo- or hyper-frontal, and to activation or medication status differences. Differences are also evident, for example, in the common symptom cluster in medicated resting (Liddle *et al.*, 1992) or un-medicated activated (Schroder *et al.*, 1995) patients, which has been located in the left parahippocampal gyrus (Friston *et al.*, 1992b) and the anterior cingulate respectively.

Two groups have also examined the pattern of inter-regional correlations in unmedicated patients; the first reporting more positive inter-correlations of CMRgl between neo-, sub- and limbo-cortical regions in patients than in controls at rest (Wiesel *et al.*, 1987b), and the second finding fewer positive inter-correlations between frontal and temporal cortex and subcortical structures whilst performing the CPT (Katz *et al.*, 1996). Finally, there have been attempts to link hypofrontality with CT structural measures, with two studies found no association with CT rated cerebral atrophy (DeLisi *et al.*, 1985a; Wiesel *et al.*, 1987a) but one reporting an association with ventriculomegaly and sylvian fissure enlargement (Kling *et al.*, 1986).

1.4.4.4 Receptor binding studies

As already described, these studies can be used to quantify receptor numbers and to image the effects of drugs in the brain. Seminal work in the 1970's had shown that the potency of a drug in binding to dopamine receptors was very strongly correlated with the dosage required in clinical practice (Seeman *et al.*, 1976; Creese *et al.*, 1976) - one of the main pillars of the 'dopamine hypothesis of schizophrenia'. Subsequent PET studies have shown that conventional doses of typical neuroleptics result in 70-90% D2 blockade, with higher occupancy in those with extra-pyramidal side effects, while the atypical neuroleptic clozapine is associated with only 40-60% occupancy (Farde *et al.*, 1992). With the development of more receptor ligands such studies may help in the rational development of new treatments for schizophrenia, but they have already begun to shed light on the pathophysiology of the disorder.

Post-mortem studies found increased densities (Bmax) of dopamine receptors in deceased patients with schizophrenia (Lee *et al.*, 1978; Owen *et al.*, 1978; Seeman *et al.*, 1984) but these changes could have been attributable to antipsychotic medication effects and in vivo PET studies have been able to examine this possibility. The ideal ligand needs to be selective, saturable and bind with high affinity so as to give anatomical and neurochemical specificity (Sedvall *et al.*, 1986); such as the relatively selective (labelled) dopamine binding drugs ^{11}C-raclopride and ^{11}C-3N-methylspiperone (NMSP). Wong *et al.* (1986) reported 2-3 fold higher D2 receptor densities in the caudate nucleus of both treated and untreated patient groups using NMSP. However, workers at the Karolinska institute in Sweden used the much more selective dopamine blocker raclopride (Farde *et al.*, 1985) in a larger number of never-medicated patients and found no significant difference in D2 receptor density on PET (Farde *et al.*, 1987 & 1990). Subsequent studies have failed to resolve these discrepancies. Although an independent raclopride study also failed to find significant differences in schizophrenia (Hietala *et al.*, 1994), and the NMSP results have only been internally replicated - by Tune *et al.* (1993), but not by Nordstrom

et al., (1995) - the Johns Hopkins group have suggested that Type II errors have hidden an overall increase of 65% in dopamine receptor numbers across the five studies (Gjedde *et al.*, 1995). It has also been suggested that raclopride underestimates changes in D2 receptor density (Seeman *et al.*, 1990) and that the NMSP studies may reflect an increase in the recently discovered D4 receptor rather than D2 activity (Seeman *et al.*, 1993). Two other studies have widened this research agenda by suggesting pre-synaptic abnormalities of increased fluorodopa uptake (Hietala *et al.*, 1995) and elevated dopa decarboxylase activity (Reith *et al.*, 1994) in schizophrenia. Furthermore, increased D2 binding may also be found in bipolar disorder (Pearlson *et al.*, 1995), which raises important questions about the specificity of all the findings with PET in schizophrenia.

1.4.5 ARE THE PET FINDINGS SPECIFIC TO SCHIZOPHRENIA?

Similar results (and inconsistencies) to those described above are apparent in the neuro-imaging literature in other psychiatric disorders. Most work has been done on the affective disorders, where hypofrontality has been reported by in unipolar depression (Buchsbaum et al, 1984; Cohen *et al.*, 1989b), bipolar affective disorder (Baxter *et al.*, 1985) or both (Baxter *et al.*, 1989), and reduced metabolism in the caudate nucleus is a fairly consistently finding in studies of depressed patients (Buchsbaum *et al.*, 1984; Baxter *et al.*, 1985). In addition, increases in subcortical metabolism have been repeatedly demonstrated in obsessive-compulsive disorder, which normalise after successful behavioural treatment (Schwartz et al., 1996). Anxiety states are also associated with PET scan changes with, for example, parahippocampal gyrus abnormalities in panic disorder (Reiman *et al.*, 1984, 1986 & 1989) and rCBF increases in limbic regions on symptom provocation in phobias (Rauch *et al.*, 1995) and post-traumatic disorder (Rauch *et al.*, 1996). Hypofrontality has also been described in anorexia nervosa (Delvenne *et al.*, 1995). Although these findings are nothing like as well replicated as in schizophrenia, there are far fewer relevant studies. As well as questioning specificity, they raise important methodological issues - such as the necessity to exclude co-morbid patients. Moreover, given recent reports of mood induction leading to limbic and paralimbic changes in metabolism (e.g. George *et al.*, 1995), arousal or sadness during scanning are likely to confound the results obtained - particularly in resting studies.

Finally, intriguing evidence for possible similarities in the neurobiology underlying sub-types of the major psychoses has come from an opportunistic study from London - where poverty of speech was associated with left sided hypofrontality independent of diagnosis in 40 patients with depression and 30 with schizophrenia (Dolan *et al.*, 1993).

1.4.6 CONCLUSIONS FROM PET STUDIES IN SCHIZOPHRENIA

The resting PET studies, therefore, do generally report a hypofrontality in schizophrenia that does not appear to be attributable to the effects of medication, while putative abnormalities in other regions are less well replicated and more influenced by medication status. Activation experiments, as with SPET, provide almost unanimous support for functional abnormalities, although the exact direction and location of these appears to critically depend on methodological factors such as the task employed, scanning technique and clinical status of the subjects. Deficits in frontal and temporal rCBF or metabolism seem to be linked to negative and positive symptoms respectively, but there is a gradually increasing awareness that such neuroanatomical localisation is simplistic and ignores likely abnormalities in the connectivity between these and other brain regions. Receptor binding studies not only promise a clear clinical application of neuroimaging - in drug development and monitoring - but also suggest a possible pathophysiological mechanism of increased dopamine receptor activity in schizophrenia. Inconsistent results in these research areas are understandable given the oft-cited 'heterogeneity' of the disease and its manifestations, and the small sample sizes in most studies; but there is some evidence that putative abnormalities are not specific to schizophrenia. Symptom based research has much to commend it, in terms of potentially identifying the neural substrates of particular phenomena, but it should not be surprising if it proves difficult to tease apart diagnostic groups on the basis of clinical features that are similar across the 'functional' psychoses. Future studies must therefore concentrate on these issues while remaining alert to the fact that the longitudinal course of schizophrenia and the affective disorders was the original basis of their distinction and remains one of the most reliable ways of clinically differentiating them. PET and SPET are less suitable techniques for monitoring changes over time than some of the less invasive methods which are currently finding their earliest applications in neuropsychiatric research (see Chapter 4).

CHAPTER 2

STUDY I

MAGNETIC RESONANCE IMAGING, SINGLE PHOTON EMISSION TOMOGRAPHY AND NEUROPSYCHOLOGICAL ASSESSMENT IN TREATMENT RESPONSIVE AND TREATMENT RESISTANT SCHIZOPHRENIA

2.1 INTRODUCTION

Kraepelin first distinguished the functional psychoses on the basis of outcome, characterising Dementia Praecox as a progressively deteriorating condition, but came to recognise that some patients - 13% of his own series - reached an apparently full recovery (Kraepelin, 1919). Outcome predictors have been described since the seminal work of Vaillant (1964), but many of the features associated with illnesses of a good outcome - such as acute onset, older age, good pre-morbid psychosocial adjustment, clear precipitants and affective features - also indicate an "atypical" nature to the psychosis (Kasanin, 1933; Langfeldt, 1960). In the modern era, treatment response is a more immediate concern than overall outcome; with repeated confirmations that medication has a variable effect in schizophrenia. A substantial number of patients will make a virtually complete symptomatic recovery (Jablensky *et al.*, 1992), while repeated trials have found that up to 25% of patients derive little and some 10% no benefit from typical neuroleptic drug therapy (Davis, 1976), and 6-8% fail to respond to many months or years of intensive antipsychotic treatment (MacMillan *et al.*, 1986; May *et al.*, 1988). Optimal prediction of treatment response has an obvious relevance in the management of schizophrenia.

The interplay between prognostic features of the illness and treatment response has been little studied, and they may have differing influences on overall outcome in clinical practice. For example, long-term outcome may relate more to the personal, social and historical characteristics of individual sufferers (Vaillant, 1964), whereas treatment response may be more dependent upon biological factors (Lieberman & Sobel, 1993). The conventional view is that drug treatment can override, at least partly, the usual prognostic effect of the static demographic variables (May & Goldberg, 1978). It is therefore tempting to speculate that inter-individual differences in response - and the pattern of its associations with other clinically and biologically relevant features of schizophrenia - may reflect the heterogeneity of the underlying disease(s), serve as a

means of identifying sub-types and shed light on the pathophysiology of the illness. Recent developments in brain imaging and neuropsychological measures of brain function have increased the possibilities for investigations in this area.

A number of research groups have made preliminary examinations of the biological associations of outcome or treatment response. CT studies have used the relatively insensitive area measure of the Ventricle-Brain Ratio (VBR), in 'good' and 'poor' patient groups divided on an arbitrary basis, and delivered inconsistent results as to whether there is a significant relationship between abnormal morphology and treatment response (e.g. Weinberger *et al.*, 1980; Nasrallah *et al.*, 1983a), or outcome (e.g. Kolakowska *et al.*, 1985; Losonczy *et al.*, 1986). MRI studies have occasionally described an association between large lateral ventricles and poor outcome (Johnstone *et al.*, 1989b; DeLisi *et al.*, 1992), but usually as a *post hoc* correlation. Functional brain imaging techniques, such as SPET and PET, have repeatedly demonstrated that higher negative symptom scores, which may be indicative of a worse outcome, are commonly associated with hypofrontality (e.g. Liddle *et al.*, 1992; Ebmeier *et al.*, 1993), particularly in chronic patients, but few have specifically examined outcome or treatment response. Finally, several researchers have identified cognitive deficits in schizophrenia, and found such impairments to be associated with a poor outcome (Johnstone *et al.*, 1978; Golden *et al.*, 1980), although this could be partly attributable to differences in motivation or concentration associated with varying degrees of symptomatology or medication.

The purpose of this study was to use such techniques, in *a priori* dichotomised patient groups, to identify the associations of treatment response. MRI, SPET and a comprehensive neuropsychological test battery were employed to test the hypotheses that treatment resistant patients would show more evidence of structural abnormality, functional underactivity and cognitive deficit than treatment responsive patients.

The specific hypotheses to be tested, and their justification, are as follows:

1. MRI - The previous literature, as reviewed in Chapter 1, suggests that the brain regions most abnormal in schizophrenia are whole brain, the lateral and third ventricles, left and right temporal lobes, and mesial temporal lobe structures such as the amygdala and hippocampus. Greater degrees of morphological abnormality are generally associated with more clinical disturbance. In particular, given that the greatest changes are likely to be found in mesial temporal lobe structures, and that these are most likely to be associated with the positive symptoms that characteristically respond best to antipsychotic medication, the specific prediction is that the hippocampus volume will be smaller in treatment resistant than responsive patients.
2. SPET - Similarly, given that patients with schizophrenia are most commonly found to be 'hypofrontal' as compared to normal controls, and that more severe symptoms are generally associated with greater functional imaging abnormality, the specific prediction is that frontal regions will show reduced tracer uptake in treatment resistant as compared to responsive patients.
3. Neuropsychology - There is less of a literature on the neuropsychology of schizophrenia and the association with symptoms, but the current consensus is that deficits in attention and memory are most reliably detected beyond what would be expected through general intellectual impairment. Accordingly, the best prediction is that treatment resistant patients will show greater impairment on attention and memory tasks - after taking global intellectual ability into account - than treatment responsive subjects.

2.2 METHODS

2.2.1 Subjects

Forty patients who satisfied DSM-III-R criteria (American Psychiatric Association, 1987) for Schizophrenia or Schizophreniform disorder were recruited from in- and out-patient populations at the Royal Edinburgh Hospital and associated hospitals. Two dichotomous patient groups were sought, treatment responsive and treatment resistant, according to the descriptive criteria for degree of Treatment Resistance proposed by May et al. (1988). These criteria describe six levels of treatment resistance, varying between "total remission within a week, whatever treatment is given (Level 1)" to "failure to respond to any useful extent after six months' hospital treatment (Level 6)" (May et al, 1988). In practice, no patients were found to satisfy these extreme levels as remission did not occur within one week in those satisfying criteria for schizophrenia and facilities to measure plasma neuroleptic levels (as required for Level 6) were unavailable. The twenty treatment responsive patients were those "...who respond well within one month...able to return to the same social situation as before...with little if any residual scarring (Level 2)" or, at worst, "patients who show a major reduction of symptoms within a month...(some) residual schizophrenic disorder...able to return to earlier social existence...(but with) reduced ability to study or work (Level 3)". The twenty patients designated as treatment resistant all showed "psychotic symptoms or disturbed behaviour (that) does not remit...such that they will remain for a long while in hospital or some alternative from of caring milieu (Level 5)". Thus, there were no patients at level 4. The selection process was designed to yield two groups of twenty patients each, who were matched for sex (ten male and ten female in each group), age (within 6 years) and duration of illness (within 6 years). Patients were excluded if they suffered from any neurological condition, current substance abuse or major depression, and all women had a pregnancy test before the scans.

2.2.2 Clinical Assessments

All 40 subjects underwent a detailed clinical examination including: a structured psychiatric interview, the Present State Examination (Wing *et al.*, 1974); a standardised rating of current symptomatology, the Manchester Symptom Scale (Krawiecka *et al.*, 1977); and a brief neurological examination to detect evidence of dyskinesia on the Abnormal Involuntary Movement Scale (AIMS) and the Targeting Abnormal Kinetic Effects (TAKE) scale (Wojcik *et al.*, 1980). This was supplemented by information from the patients' psychiatric casenotes to complete the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L; Spitzer & Endicott, 1978), for Research Diagnostic Criteria (RDC; Feighner *et al.*, 1972) and a modified version of the DHSS Survey form (Johnstone, 1991).

These assessments gave a detailed record of the patients' psychiatric history - in particular, of age at illness onset, duration of illness, number and duration of hospital admissions - parental social class and a comprehensive account of medication exposure. Age of onset was defined as the age at first contact with a psychiatrist who recorded sufficient features to satisfy DSM-III-R diagnostic criteria for schizophrenia; the duration of illness taken from this date until the beginning of the investigation in January 1992. Exposure to psychotropic medication, in particular to antipsychotic and anticholinergic agents, was recorded as the current dose in chlorpromazine and procyclidene equivalents.

Additional measurements of illness outcome were made from interview and casenote information. Social outcome, in terms of self care, employment and acceptability of behaviour, was assessed on the rating scale devised by Cooper (1961), while global outcome was measured on the McGlashan cross-sectional and follow-up scales (McGlashan, 1984).

2.2.3 Magnetic Resonance Imaging

2.2.3.1 Image Acquisition

All 40 patients underwent MRI scanning on a 1.0 tesla Siemens (Erlangen, Germany) scanner. Mid-line sagittal localisation was followed by two sequences to image the whole brain. A "Turboflash" sequence, a 3D-FLASH collection 500ms after a spin inversion (TI = 500ms), with a relaxation delay of one second, was employed to acquire an image that could be reconstructed in three dimensions. A Spin Echo (SE) dual-echo scan was also conducted, with a repetition time of 3565ms, and echo times of 20ms to obtain a proton density weighted image and 90ms for a T_2-weighted image (SE 3565/20-90). The 3D-FLASH sequence was collected as 128 contiguous 1.56mm thick coronal slices; with flip angle 10 degrees, repetition time 10ms, echo time 4ms, field of view 255mm, and a relaxation delay of one second. The SE scan generated 31 contiguous 5mm thick axial slices in the Talairach plane; with flip angle 90 degrees and field of view 250 mm. The scans had acquisition matrices of 130 x 256 and 192 x 256 pixels respectively; both being interpolated to 256 x 256 on transfer to a Sun work station. Thus, the voxel size was 0.996 x 0.996 x 1.56 mm on the 3D-FLASH image and 0.976 x 0.976 x 5 mm on the SE image. Regular phantom measurements over the fifteen months of the study ensured that these sequences remained reliable.

2.2.3.2 Visual Assessment

A clinical neuroradiologist (CGS - see acknowledgements) examined the MRI scans for structural abnormalities and motion artefact. Two female subjects, both treatment responsive, were excluded from the study due to a previously undiagnosed pituitary tumour and left hemisphere infarct respectively, and two additional patients recruited. One male subject was re-scanned as his first scan was severely degraded by movement. A standardised clinical assessment was made of the severity of cerebral atrophy, an "atrophy score", on a seven-point scale (0 to 6), as indicated by the degree of

sulcal widening, ventricular size and shape, the relative size of the brain to the cranium, and the patients' age. High Intensity Signal (HIS) lesions were coded as present or absent, and their location and numbers noted - being distinguished from Virchow-Robin spaces by comparison between the proton density and T2 weighted images.

2.2.3.3 Volumetric measurements

Image processing was carried out on Sun Microsystems workstations using the software package "Analyze" (Mayo Foundation, Rochester, USA) to outline and compute volumes of the neuroanatomical structures of interest. Structures were identified with the assistance of a MRI atlas (Duvernoy, 1991), and volumes were calculated by summing voxels over all slices included. Specific regions of interest were selected a priori as: pre-frontal lobes (left and right), temporal lobes (left and right), hippocampi (left and right), whole brain, intracranial cerebrospinal fluid (CSF), lateral ventricles (left and right), and third and fourth ventricles.

The pre-frontal lobes were defined as extending from the frontal pole to the last slice before the appearance of the fibres of the genu of the corpus callosum (after Suddath *et al.*, 1990); the temporal lobes defined as extending from temporal pole to the last slice containing fibres of the crux of the fornix, and the hippocampi defined as extending from the appearance of the temporal stem to the last slice containing the fornix crux fibres (after Shenton *et al.*, 1992). The remaining regions of interest were outlined using naturalistic boundaries (after Suddath *et al.*, 1990). The third and fourth ventricle volumes were estimated in combination, together with the cerebral aqueduct, as it was difficult to reliably distinguish their posterior boundaries from the suprapineal and cerebellar cisterns respectively. The 3D-FLASH scans were used for all measurements, except the whole brain and intracranial CSF volumes which were calculated from the SE 3565/20-90 scans after ensuring that the whole brain volumes were closely related by both techniques (inter-scan correlation r = 0.96; mean difference 30.8 cc, standard deviation (sd) 32.3).

Comparisons of structure volumes between groups were made both uncorrected and corrected (as a ratio) for whole brain volume, to control for variations in head size.

2.2.3.4 Inter-Rater Reliability

The assistance of two trained medics was enlisted to conduct the volumetric measurements, as this took approximately six hours for each brain analysed. All three volume raters remained blind to group membership. The author (SML) calculated all ventricular volumes, another rater (GTI) all whole brain and intracranial CSF volumes, and the third (CGS) the hippocampi, while two raters (SML and GTI) estimated pre-frontal and temporal volumes. All three raters examined ten pre-frontal and temporal lobes to determine inter-rater reliabilities (inter-rater correlation SML-GTI $r = 0.93$, mean difference 1.07cc, sd 4.7; SML-CGS $r=0.90$, mean difference 1.95cc, sd 3.7).

2.2.4 Single Photon Emission Tomography

SPET imaging was performed on a head dedicated SME-Neuro 900 12-detector Strichman scanner, using ^{99m}Tc-Exametazime (HMPAO) to measure regional cerebral perfusion. Tracer uptake was measured as count density on slices at 5mm intervals, extending the full length of the brain, a total of 14 to 18 slices per subject. Three slices were used in this study: at the mid-ventricular level (including the basal ganglia) 4cm above the orbito-meatal line (OML), and 6cm and 8cm above the OML. A standardised brain template, derived from a brain atlas (Talairach *et al.*, 1988), was symmetrically and linearly transformed to fit the outline of the brain defined by 40% of the images' intensity spectrum, by a physicist blinded to scan identity and indifferent to the experimental result. Although this method does not take inter-individual anatomical differences into account, it leaves the relative relationship of regions of interest to one another intact and provides a reliable method for determining relative uptake patterns (Ebmeier *et al.*, 1991). Regional count densities were reconstructed with Neuro-900 software (version 2.66) and analysed using the Statistical Package for the Social Sciences (SPSS) for Apple Mac, version 4.0. Group comparisons were conducted after normalising both for whole slice and occipital uptake; the 36 regions of interest (18 left and right) examined are shown with the results.

2.2.5 Neuropsychological Test Battery

Comprehensive testing was undertaken with a wide variety of tasks chosen for ease of application. Pen and paper tasks included: a measure of pre-morbid intellectual ability, the National Adult Reading Test (NART; Nelson, 1982); a measure of current IQ, the Quick Test (Ammons & Ammons, 1962); the Mini-Mental State Examination, as a measure of global intellectual functioning (MMSE; Folstein *et al.*, 1975); an assessment of attention/working memory, the Digit Span (forwards and backwards - Randt memory battery version A) and of psychomotor speed, Digit Symbol Substitution, from the Wechsler Adult Intelligence Scale - Revised (WAIS-R; Wechsler, 1981). Tests of executive functioning included: Verbal Fluency, or word production, for animals (Animal Naming Set Test, Isaacs & Kennie, 1973) and for words beginning with the letter 'A' (Controlled Word Association Test, Benton, 1978) in 60 seconds; the Stroop test (Stroop, 1935); and Trails 'A' and 'B' (Reitan, 1958). The Annett scale was chosen to measure handedness (Annett, 1970). The Rivermead Behavioural Memory Test (RBMT; Wilson *et al.*, 1985) was used as an index of episodic memory. Selected measures from the Cambridge Neuropsychological Testing Automated Battery (CANTAB; Owen *et al.*, 1990) were also employed: Spatial and Pattern Recognition, and the Delayed Matching to Sample tasks as tests of memory, and the Continuous Performance Test as a measure of sustained attention. Finally, the tester rated the patients attention and co-operation on two five-point scales (after Shakow, 1981).

2.2.6 Timing of Investigations and Data Analysis

Once the diagnosis was confirmed and group membership assigned, the usual sequence of investigation was from MRI to SPET to neuropsychology to clinical assessment. The SPET scan generally followed MRI within one week (median interval = 6 days). The neuropsychological and clinical assessments were usually completed on the same day, in two sittings, within a few days of the SPET scan (median interval = 6 days).

The results were largely analysed by SPSS for Mac 4.0. As age, sex and duration of illness were matched between groups at the design stage, the effects of these variables were not examined. In order to estimate the probability that the pattern of structural and functional group differences had arisen by chance a multivariate analysis of variance was conducted treating the 11 MRI regional volumes and 36 SPET regional tracer uptake ratios as repeated measures. MRI statistical analyses were conducted on both absolute and corrected (for whole brain) volumes, while SPET analyses were conducted on corrected (to whole slice and occipital) uptake ratios. The effects of laterality and region on structure volumes were examined as two "within subjects' factors", in addition to the primary comparison "between subjects" of treatment response group membership. This was followed by a *post hoc* t-test for individual regions of interest in both the MRI and SPET scans. Effect sizes were calculated for between group differences in MRI volumes, by dividing the volume difference by the larger of the two standard deviation (Gore & Altman, 1982).

Neuropsychological test results were compared between the response groups by analysis of variance (ANOVA); possible confounders being controlled for with an analysis of co-variance (ANCOVA).

The subjective atrophy score ratings and HIS lesion numbers were compared with the Mantel-Haenszel test for linear association. They were then coded as present or absent to allow examination of this association by univariate logistic regression. Spearman

correlation coefficients were computed between these anomaly scores and the symptom ratings, regional MRI volumes and neuropsychology results.

Associations between clinical and outcome variables, with neuropsychological variables and regional volumes, were also examined by two-tailed Spearman rank correlation coefficients. To conduct correlations between numerous clinical/neuropsychological results and the large number of SPET (and MRI) variables, the former were factor analysed. A principal components analysis identified initial factors, a varimax rotation was performed, and factor scores were calculated by regression. These factors were then correlated, by the Spearman rank method, with the SPET and MRI results.

2.3 RESULTS

2.3.1 Subjects, demographics and clinical characteristics

Approximately three patients were approached for each one who was suitable and consented to participate. This limited the dichotomy of treatment response between groups further, as very poor responders were often too unwell to comply with the detailed assessments, while very good responders were sometimes not under active follow-up and reluctant to return to the hospital.

Of those who agreed to participate, the DSM-III-R diagnostic categories were: Schizophreniform Psychosis (N=2) and Schizophrenia (N=38). Sub-categories of Schizophrenia were: Paranoid (N=19), Undifferentiated (N=10), Disorganised (N=8), and Catatonic (N=1), and 36 suffered from DSM-III-R Chronic Schizophrenia. Thirty-five patients also satisfied RDC criteria for Schizophrenia, the others being Schizoaffective (N=3) or Schizophreniform (N=2). The patients were clinically stable at the time of the investigations, so that the effects of acute relapse and/or large doses of medication were minimised. Table 2.1 (overleaf) describes the patients by their demographics, relevant historical details and current medication levels. The matching of patients for sex, age and illness duration was satisfactory, although treatment resistant patients were slightly younger and yet had been ill for longer, indicating an earlier age at onset in this group. As would be expected, the mean number of admissions, total time spent in hospital and current medication dosage were substantially higher in treatment resistant patients. Table 2.2 (two pages overleaf) details the clinical picture at the time of testing, by measures of symptom severity, outcome and abnormal movements. The patient groups differed substantially on most individual symptom measures and the total scores, and all outcome measures. In addition, 14 of the responsive patients were employed or full-time students (and a further three were active housewives) as compared to none of the resistant subjects. Statistically significant differences were found between the response groups on the AIMS (Mann-Whitney U=103.5, P=0.006), but not the TAKE (U=139.5, P=0.1).

Table 2.1 - Clinical characteristics of treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations)

	RESPONSIVE	RESISTANT	Probability of the difference
SEX	10 Male 10 Female	10 Male 10 Female	Matched
AGE (years)	36.5 (9.9) range 22-54	34.7 (10.3) range 19-53	Matched
ILLNESS DURATION (months)	139.3 (105.5) range 9-355	150.8 (106.0) range 7-333	Matched
YEARS IN EDUCATION	14.0 (2.8)	10.9 (1.2)	$P < 0.001$ $df = 38, t = 4.4$
PATERNAL OCCUPATION (Social Class I-VI)	2.6 (0.8)	2.9 (0.5)	$P = 0.4$ Likelihood ratio = 1.8
NUMBER of ADMISSIONS	4.9 (4.7)	10.4 (6.5)	$P < 0.005$ $df = 38, t = -3.1$
HOSPITALISATION TIME (months)	6.6 (7.1)	57.1 (87.4)	$P < 0.002$ $df = 38, t = -2.6$
ANTIPSYCHOTIC DOSAGE (Chlorpromazine equivalents)	268 (274)	902 (669)	$P < 0.001$ $df = 38, t = -3.8$
ANTICHOLINERGIC DOSE (Procyclidine equivalents)	3.0 (6.4)	3.3 (4.7)	$P = 0.9$ $df = 38, t = -0.2$

Table 2.2 - Symptom and outcome measure scores in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations)

	RESPONSIVE	RESISTANT
KRAWIECKA TOTAL SCORES	3.9 (3.3)	11.8 (5.1)
KRAWIECKA DEPRESSION	0.5 (0.6)	1.0 (0.9)
KRAWIECKA ANXIETY	0.8 (0.9)	1.1 (1.1)
KRAWIECKA DELUSIONS	0.6 (1.0)	3.4 (1.1)
KRAWIECKA HALLUCINATIONS	0.2 (0.8)	2.5 (1.8)
KRAWIECKA SPEECH IRRELEVANCE	0.3 (0.5)	0.8 (1.2)
KRAWIECKA POVERTY of SPEECH	0.2 (0.5)	0.4 (0.6)
KRAWIECKA FLAT AFFECT	0.6 (0.9)	1.2 (1.1)
KRAWIECKA INCONGRUITY	0.4 (0.9)	0.7 (1.2)
KRAWIECKA RETARDATION	0.2 (0.5)	0.6 (0.8)
POSITIVE SYMPTOMS TOTAL SCORE	0.4 (0.6)	1.8 (0.9)
NEGATIVE SYMPTOMS TOTAL SCORE	0.5 (0.4)	0.9 (0.5)
COOPER'S OUTCOME SCALE	4.8 (0.8)	1.8 (0.5)
McGLASHAN'S Cross-Sectional Outcome	15.4 (2.6)	5.6 (2.1)
McGLASHAN'S Follow-Up Outcome	15.4 (2.0)	6.0 (2.2)
AIMS	1.0 (1.7)	2.8 (2.4)
TAKE	2.2 (2.1)	3.4 (2.0)

2.3.2 MRI Results

2.3.2.1 MRI Volumetric Measurements

The hippocampi could not be reliably measured in two male cases due to movement artefact, but the remaining structures were thought to be reliably identifiable in all scans. The mean height of the resistant patients, at 167.8 cm, was lower but not significantly different from that of the responsive patients, at 169.4cm (P=0.6). Analysis between response groups by MANOVA found no significant differences in the volumes of any measured structure, comparing either raw volumes ($F_{1,36}$=1.1, P=0.3), or those normalised to whole brain volume ($F_{1,36}$=0.2, P=0.9). Table 2.3 (overleaf) shows the absolute volumes of the structures measured, together with effect sizes of the differences between response groups. Almost all structures are smaller in the treatment resistant group, with only minor exceptions of the left pre-frontal lobe and the third/fourth ventricles. There was no interaction between response and lobe ($F_{1,36}$=2.0, P=0.2), but a tendency to one between response and side ($F_{1,36}$=3.0, P=0.09). Examining table 2.3 this interaction is likely to reflect the smaller difference between the left and right volumes of the lateral ventricles, temporal lobes and particularly pre-frontal lobes in the resistant as compared to the responsive patients; but this possible effect was not examined statistically as no tilt correction was employed prior to image analysis.

Post hoc paired t-tests, across all subjects, revealed smaller left than right sided hippocampi (two-tailed t=3.03, P=0.004) and temporal lobes (two-tailed t=1.93, P=0.06). Left handed subjects (N=4), were found to have lower volumes of all structures than the right-handers (N=35; 1 ambidextrous), but this difference was only statistically significant in the left temporal lobe (raw volumes 68.2 versus 76.6 cc; two-tailed t=3.26, P=0.01), for both raw and corrected volumes.

Table 2.3 - Raw volumes (cc) on MRI in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations), and effect sizes (in standard deviation units).

	RESPONSIVE	RESISTANT	EFFECT SIZE
WHOLE BRAIN	1196.3 (113.7)	1142.8 (131.2)	0.41
INTRACRANIAL CSF	218.8 (44.2)	207.0 (77.6)	0.15
LEFT TEMPORAL LOBE	77.4 (8.2)	73.4 (10.8)	0.37
RIGHT TEMPORAL LOBE	80.3 (10.2)	75.5 (10.5)	0.46
LEFT HIPPOCAMPUS	5.3 (0.7)	5.1 (0.7)*	0.29
RIGHT HIPPOCAMPUS	5.5 (0.6)	5.3 (0.7)*	0.29
LEFT PRE-FRONTAL LOBE	61.0 (8.3)	61.2 (11.8)	-0.02
RIGHT PRE-FRONTAL LOBE	63.7 (8.2)	61.8 (11.1)	0.17
LEFT LATERAL VENTRICLE	9.1 (4.5)	8.5 (3.5)	0.17
RIGHT LATERAL VENTRICLE	8.8 (4.0)	8.0 (3.2)	0.25
THIRD & FOURTH VENTRICLES	4.1 (1.3)	4.2 (1.3)	-0.08

***N=18 as two male hippocampi excluded due to motion artefact.**

2.3.2.2 MRI Visual Assessment

Thirty-three (82%) of the patients showed some ('none-mild' or greater) degree of generalised cerebral atrophy, which was at least 'mild' (score of 2 or more) in 21 (52%). Almost all (95%) of the treatment-resistant patients had some atrophy, as compared to 14 (60%) of the responsive cases, but this difference was not statistically significant (M-H value = 1.6, P=0.2). However, using the more powerful statistical technique of logistic regression with atrophy dichotomised into none or some, a strong tendency was found to an association between treatment response and atrophy (P=0.06) with the resistant patients having a substantially elevated risk (odds ratio = 2.85, 95% confidence interval 0.94-8.69).

Fifteen (38%) of the patients had at least one HIS lesion (range 0-4). These were widely and bilaterally distributed, in the cortex, deep white matter, periventricular region and subcortical areas. They were identified in 9 (45%) resistant and 6 (30%) responsive patients, with no suggestion of a significant difference by chi-square (M-H value = 0.7, P=0.4) or logistic regression (OR=1.4, P=0.3) analyses with dichotomisation around none or at least one lesion. However, 5 (25%) of the resistant patients had at least three HIS lesions, as compared to 2 (10%) of the responsive patients.

Finally, an unexpected observation from visual assessment of the scans was the frequency of appearances suggesting inflammation of the lining of the paranasal sinuses. The ethmoid sinus was affected in 72%, the maxillary sinus in 20%, the frontal sinus in 18% and the sphenoidal sinus in 10%. However, the prevalence of sinusitis was identical in both treatment resistant and responsive patients, at 90%, and is probably related to the fact that 33 (82%) of the patients were current cigarette smokers.

2.3.3 SPET scan results

The overall effect of treatment response on regional uptake ratios failed to reach statistical significance by MANOVA, whether uptake was normalised to the whole slice ($F_{1,38}$=0.98, P=0.5) or occipital uptake ($F_{1,38}$=2.06, P=0.3). Table 2.4 (overleaf) gives the uptake ratios, corrected for whole slice uptake, in the 36 regions of interest from the three slices chosen for analysis in this study.

Table 2.4 - SPET regional uptake of 99mTc-Exametazime, normalised to the whole slice, in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations).

	LEFT		RIGHT	
	RESPONSIVE	RESISTANT	RESPONSIVE	RESISTANT
Lower Slice (4cm above OML)				
Frontal	0.96 (.04)	0.95 (.05)	0.99 (.03)	0.97 (.05)
Anterior Temporal	1.03 (.06)	1.02 (.07)	1.09 (.05)	1.06 (.06)
Posterior Temporal	1.04 (.06)	1.03 (.04)	1.07 (.04)	1.06 (.06)
Occipital	1.02 (.04)	1.02 (.06)	1.03 (.04)	1.02 (.05)
Calcarine	1.17 (.08)	1.19 (.09)	1.18 (.06)	1.19 (.08)
Anterior Cingulate	1.02 (.09)	1.01 (.08)	1.08 (.08)	1.05 (.08)
Posterior Cingulate	0.91 (.08)	0.95 (.08)	0.96 (.11)	0.98 (.10)
Caudate	0.90 (.09)	0.92 (.12)	0.95 (.11)	0.94 (.08)
Putamen	1.10 (.06)	1.08 (.06)	1.08 (.07)	1.06 (.06)
Thalamus	1.04 (.04)	1.03 (.06)	1.04 (.05)	1.05 (.06)
Middle Slice (6cm above OML)				
Frontal	0.95 (.04)	0.94 (.04)	0.97 (.04)	0.96 (.04)
Parietal	1.00 (.04)	1.01 (.04)	1.03 (.04)	1.02 (.03)
Occipital	1.04 (.06)	1.04 (.06)	1.06 (.07)	1.04 (.06)
Anterior Cingulate	1.08 (.08)	1.05 (.06)	1.09 (.06)	1.05 (.07)
Posterior Cingulate	1.21 (.10)	1.24 (.07)	1.22 (.06)	1.25 (.06)
Upper Slice (8cm above OML)				
Frontal	0.87 (.05)	0.89 (.03)	0.88 (.06)	0.91 (.04)
Parietal	0.92 (.06)	0.95 (.06)	0.96 (.05)	0.97 (.04)
Occipital	0.96 (.06)	1.00 (.06)	0.98 (.07)	1.01 (.05)

2.3.4 Neuropsychology test results

Some patients did not complete all the testing, but only one refused to do all the tests. The detailed results are presented in three tables on consecutive pages overleaf, according to whether the tests primarily measured global (Table 2.4), executive (2.5) or memory functioning (2.6). As shown in these tables, several statistically significant differences emerged between the two response groups, indicating poorer functioning in the resistant patient group. However, these deficits could be attributable to clinical differences between the resistant and responsive patients, such as in pre-morbid functioning and neuroleptic exposure. To control for the former, all the differentiating tests were re-analysed co-varying for the number of years spent in full time education and only one measure remained which clearly distinguished, at a high level of statistical significance, between responsive and resistant patients - the Rivermead Behavioural Memory Test - Profile Score (RPS, $F_{1,35}$=9.7, P=0.004). This test showed a statistically significant difference between the groups, even when current IQ ($F_{1,36}$=9.5, P=0.005), global intellectual functioning ($F_{1,35}$=8.5, P=0.007), and current antipsychotic medication levels ($F_{1,36}$=11.8, P=0.002) were taken into account; and the current dose of anticholinergic drugs were very similar in the responsive and resistant subjects. Table 2.7 (four pages overleaf) shows the differentiating neuropsychological test results, and the between group differences before and after controlling for years spent in education to show the magnitude of the effect.

Table 2.4 - Global intellectual functioning in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations)

	RESPONSIVE	RESISTANT	F value	P value
NART IQ (WAIS equivalent)	114.5 (10.3)	101.2 (9.5)	$F_{1,37} = 17.6$	$P < 0.001$
QUICK IQ	107.4 (18.0)	89.1 (14.9)	$F_{1,37} = 12.0$	$P = 0.001$
IQ DECLINE	7.0 (13.0)	12.1 (10.2)	$F_{1,37} = 1.3$	$P = 0.2$
MINI-MENTAL STATE EXAM	28.3 (1.8)	25.1 (3.7)	$F_{1,37} = 10.0$	$P = 0.003$
DIGIT SYMBOL SUBSTITUTION	8.6 (2.4)	6.4 (2.0)	$F_{1,35} = 8.9$	$P = 0.005$
ATTENTION	4.7 (0.6)	3.9 (1.1)	$F_{1,37} = 8.3$	$P = 0.006$
CO-OPERATION	4.5 (0.5)	4.2 (0.8)	$F_{1,37} = 9.1$	$P = 0.005$

Table 2.5 - Executive functioning in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations)

	RESPONSIVE	RESISTANT	F value	P value
CONTINUOUS PERFORMANCE TEST - F (failed response, omissions)	0.2 (0.4)	0.7 (1.6)	$F_{1,33} = 1.6$	P = 0.2
CONTINUOUS PERFORMANCE TEST - I (inappropriate response, commissions)	1.0 (1.4)	3.3 (3.3)	$F_{1,33} = 6.6$	P = 0.015
STROOP TEST W-C (word-colour, errors)	16.7 (17.9)	41.0 (19.5)	$F_{1,33} = 14.7$	P = 0.001
TRAILS TESTS B-A (thinking time)	49.8 (25.6)	60.4 (36.5)	$F_{1,33} = 1.0$	P = 0.3
VERBAL FLUENCY - letter 'A'	13.4 (7.5)	9.6 (5.3)	$F_{1,33} = 3.0$	P = 0.09
VERBAL FLUENCY - animals	20.2 (8.7)	14.2 (7.1)	$F_{1,33} = 4.9$	P = 0.03

Table 2.6 - Memory functioning in treatment responsive and treatment resistant patients with schizophrenia (means and standard deviations)

	RESPONSIVE	RESISTANT	F value	P value
DELAYED MATCH TO SAMPLE - SIMULTANEOUS	9.4 (0.7)	8.7 (2.0)	$F_{1,36} = 2.0$	P = 0.2
DELAYED MATCH TO SAMPLE - 0 SEC. DELAY	8.2 (1.5)	6.6 (2.5)	$F_{1,36} = 5.9$	P = 0.02
DELAYED MATCH TO SAMPLE - 4 SEC. DELAY	7.8 (1.2)	6.7 (2.5)	$F_{1,36} = 3.2$	P = 0.08
DELAYED MATCH TO SAMPLE - 12 SEC. DELAY	6.7 (1.7)	5.6 (1.9)	$F_{1,36} = 4.0$	P = 0.053
PATTERN RECOGNITION	19.3 (4.1)	17.8 (3.0)	$F_{1,36} = 1.5$	P = 0.2
SPATIAL RECOGNITION	15.4 (2.3)	13.6 (3.0)	$F_{1,36} = 4.5$	P = 0.04
DIGIT SPAN - FORWARDS	7.5 (1.4)	7.3 (1.2)	$F_{1,36} = 0.4$	P = 0.5
DIGIT SPAN - BACKWARDS	5.3 (1.9)	3.7 (1.3)	$F_{1,36} = 9.1$	P = 0.005
RIVERMEAD PROFILE SCORES	21.7 (1.9)	17.3 (3.8)	$F_{1,36} = 20.3$	P < 0.001

Table 2.7 - Neuropsychological tests which distinguished between treatment responsive and resistant schizophrenia (means and standard deviations).

	RESPONSIVE	RESISTANT	PROBABILITY (BEFORE controlling for yrs in education)	PROBABILITY (AFTER controlling for yrs in education)
Global Measures				
NART (WAIS corrected)	114.5 (10.3)	101.2 (9.5)	$F_{1,37}=17.6$, $P<0.001$	$F_{1,36}=2.4$, $P=0.1$
QUICK IQ	107.4 (18.0)	89.1 (14.9)	$F_{1,37}=12.0$, $P=0.001$	$F_{1,36}=3.4$, $P=0.075$
MINI-MENTAL STATE EXAMINATION	28.3 (1.8)	25.2 (3.7)	$F_{1,36}=10.0$, $P=0.003$	$F_{1,35}=4.1$, $P=0.052$
DIGIT SYMBOL SUBSTITUTION	8.6 (2.4)	6.4 (2.0)	$F_{1,35}=8.9$, $P=0.005$	$F_{1,34}=1.5$, $P=0.3$
Executive Functioning				
CPT-I (errors)	1.0 (1.4)	3.3 (3.3)	$F_{1,33}=6.6$, $P=0.015$	$F_{1,32}=2.4$, $P=0.1$
STROOP TEST - Word Colour (errors)	16.7 (17.9)	41.0 (19.5)	$F_{1,33}=14.7$, $P=0.001$	$F_{1,32}=2.5$, $P=0.1$
VERBAL FLUENCY - "Animals"	20.2 (8.7)	14.2 (7.1)	$F_{1,33}=4.9$, $P=0.033$	$F_{1,32}=0.3$, $P=0.6$
Memory Tests				
DIGIT SPAN - Backwards	5.3 (1.9)	3.7 (1.3)	$F_{1,36}=9.1$, $P=0.005$	$F_{1,35}=1.1$, $P=0.3$
SPATIAL RECOGNITION (CANTAB)	15.4 (2.3)	13.6 (3.0)	$F_{1,36}=4.5$, $P=0.041$	$F_{1,35}=0.8$, $P=0.4$
RIVERMEAD PROFILE SCORES	21.7 (1.9)	17.3 (3.8)	$F_{1,36}=20.3$, $P<0.001$	$F_{1,35}=9.7$, $P=0.004$

Key: CPT-I = Continuous Performance Test - Inappropriate responses (i.e. errors of commission).

2.3.5 Clinical and Biological Correlations

Exploratory correlational analyses were performed between the clinical and biological data in all 40 subjects. As shown in Table 2.8 (overleaf), Spearman rank correlations between clinical and MRI variables were fairly strong and negative between delusion ratings and temporal lobe volumes, hallucinations and the hippocampi, anxiety and the lateral ventricles; with fairly strong positive correlations between retardation and flat affect ratings and the lateral ventricle volumes. All outcome measures consistently and positively correlated with the temporal lobe volumes. Differentiating neuropsychological test variables were consistently negatively correlated with delusion and hallucination symptom scores on the Krawiecka Scale, as well as strongly and positively with the outcome measures. Notably, the clinical correlations with the Rivermead Profile Score (RPS) score were slightly higher than for other test results.

As shown in Table 2.9 (two pages overleaf), Spearman correlations between the MRI and neuropsychological variables were strongest for whole brain, left pre-frontal lobe and particularly the temporal lobe (both left and right) volumes. Measures of global intellectual functioning were generally more strongly related to MRI volumes than were the memory tests; indeed, correlations with RPS were often lower than those of both global and executive tests.

Spearman correlations between the qualitative MRI anomaly ratings and other variables of interest were rarely statistically significant. No significant correlations were found between atrophy or HIS lesion number and Krawiecka positive or negative syndrome scores, nor with the neuropsychology results. The only significant correlations with regional volumes were between atrophy and the volumes of the left ($r=.36$, $P<0.05$) and right ($r=.32$, $P<0.05$) ventricular volumes, and between the number of HIS lesions and the volumes of these same structures ($r=.33$ and .39 respectively). Of particular note, were very weak correlations between atrophy and the whole brain ($r=.10$) or intracranial CSF ($r=-.04$) volumes.

Table 2.8 - Spearman Rank correlations of MRI structure volumes and Neuropsychological tests (distinguishing groups) with clinical and outcome measures in treatment responsive and resistant schizophrenia

	Kraw. Dep.	Kraw. Anx.	Kraw. Delus.	Kraw. Halluc.	Kraw. Irrel.	Kraw. Pov.	Kraw. Flat	Kraw. Incon.	Kraw. Ret.	C'pers	McG. CS.	McG. FU.	AIMS	TAKE
Whole Brain	.12	-.26	**-.37****	-.25	-.08	.06	-.09	**.36***	-.06	.15	.20	.15	.10	-.01
CSF	-.16	-.16	-.20	**-.27***	.04	.08	.17	.18	.09	.20	.20	.25	-.00	-.09
Left Temporal Lobe	.13	-.16	**-.42****	-.24	.06	.19	.07	**.36***	.02	**.31***	**.40****	**.30***	.15	-.12
Right Temporal Lobe	-.06	**-.37***	**-.51****	**-.34***	-.04	.16	-.17	.14	-.09	**.29***	**.38****	**.28***	.23	-.18
Left Hippocampus	-.17	-.07	-.20	**-.42****	-.18	**-.32***	-.02	.25	-.13	.20	.26	**.29***	-.26	-.13
Right Hippocampus	-.12	.05	-.10	**-.33***	-.01	-.26	.04	**.44****	-.17	.18	.18	.21	**-.29***	-.16
Left Pre-Frontal Lobe	.12	.16	-.20	-.18	-.20	.04	.14	**.37***	.09	.22	.21	.21	.01	.05
Right Pre-Frontal Lobe	.07	-.21	**-.40****	**-.30***	**-.32***	-.06	-.11	.26	-.01	.24	.25	**.30***	.06	.08
Left Lateral Ventricle	-.06	**-.47****	-.13	-.19	-.19	.09	**.34***	-.02	**.27***	.08	.10	.04	.03	.07
Right Lateral Ventricle	.03	**-.29***	-.17	-.12	-.13	.15	**.47****	.07	**.38****	.02	.05	.05	-.00	.20
Third&Fourth Ventricles	.05	-.24	-.18	-.05	.03	.17	.07	.16	**.31***	-.04	.02	-.06	.13	-.23
NART (WAIS corrected)	-.07	-.06	**-.45****	**-.38****	-.23	-.01	-.01	-.15	.01	**.53*****	**.51*****	**.45****	-.08	.01
Quick IQ	.08	.05	**-.45****	**-.44****	-.21	-.04	-.01	-.01	-.11	**.48****	**.45****	**.43****	-.07	.03
MMSE	.16	-.06	**-.38****	-.22	-.04	.21	-.04	.04	-.00	**.48****	**.48****	**.34***	.05	-.02
Digit Symbol Substitution	.08	-.02	**-.33***	-.25	**-.31***	-.00	.16	.02	.12	**.41****	**.31***	**.23**	**-.32***	-.14
CPT-I (errors)	-.05	.10	**.36***	..23	.21	.00	.00	.02	.05	**-.49****	**-.41****	**-.32***	.07	.21
Stroop -Word Colour (errors)	.08	-.09	**.46****	**.40****	.21	.10	.13	.02	.18	**-.63*****	**-.56*****	**-.48****	.08	**.35***
Verbal Fluency - "Animals"	-.25	-.25	**.36***	.23	.21	.00	.00	.02	.05	**.45****	**.47****	**.47****	-.07	-.22
Digit Span - Backwards	-.05	-.08	**-.39****	**-.34***	-.07	.21	.05	-.23	.03	**.44****	**.47****	**.37***	.01	.00
Spatial Recognition (CANTAB)	.07	.20	-.21	-.20	-.10	-.10	.15	.23	-.05	**.37***	**.32***	**.36***	-.14	.11
Rivermead Profile Score	-.02	.05	**-.54*****	**-.42****	-.13	-.18	**-.27***	-.03	**-.33***	**.65*****	**.62*****	**.57*****	.00	-.11

KEY: Kraw. = Krawiecka Symptom Scores - Dep. (Depression), Anx. (Anxiety), Delus. (Delusions), Halluc. (Hallucinations), Irrel. (Irrelevance/Incoherence of Speech), Pov. (Poverty of Speech), Flat (Flat Affect), Incon. (Incongruous Affect), Ret. (Psychomotor Retardation). C'pers = Coopers Outcome Score. McG.CS. = McGlashan's Cross-Sectional Outcome Score. McG.FU. = McGlashan's Follow-Up Outcome Score. CPT-I = Continuous Performance Test Inappropriate responses (errors of commission). MMSE = Mini-Mental State Examination.

PROBABILITY: *P<0.05, **P<0.01, ***P<0.001.

Table 2.9 - Spearman Rank correlations between MRI structure volumes and Neuropsychological tests (distinguishing groups) in treatment responsive and resistant schizophrenia

	NARTw	QuickIQ	MMSE	DSS	CPT-I	Stroop	VF	DS-B	Spatial	RPS
Whole Brain	**.41****	**.45****	**.48****	**.33***	**-.34***	-.30	**.34***	**.41****	.16	.28
Intracranial CSF	.08	.09	.07	.11	-.13	-.22	.21	.09	.27	.16
Left Temporal Lobe	**.48****	**.57*****	**.52****	**.34***	**-.47****	**-.52****	**.39***	**.68*****	.30	.32
Right Temporal Lobe	**.49****	**.45****	**.48****	.32	-.27	**-.48****	.30	**.45****	-.02	.31
Left Hippocampus	-.08	.13	.09	.03	-.06	-.06	.11	-.09	.11	.02
Right Hippocampus	-.13	.11	.01	.05	.03	-.09	.05	-.01	.22	-.02
Left Pre-Frontal Lobe	**.34***	**.39***	**.34***	.28	-.31	-.29	.25	**.36***	**.34***	.28
Right Pre-Frontal Lobe	**.35***	.30	.32	**.36***	-.22	-.26	.20	.17	.11	.32
Left Lateral Ventricle	.18	.06	.29	.29	-.25	-.02	.13	**.32***	.15	-.00
Right Lateral Ventricle	.12	-.02	.14	.32	-.24	-.05	.16	.21	.27	-.02
Third & Fourth Ventricles	-.16	-.15	.04	.13	-.29	.05	-.18	-.01	-.05	-.12

KEY: NARTw = National Adult Reading Test (WAIS corrected); MMSE = Mini-Mental State Examination; DSS = Digit Symbol Substitution; CPT-I = Continuous Performance Test - Inappropriate responses (errors); Stroop = Stroop Word-Colour Test (errors); VF = Verbal Fluency - "Animals"; DS-B = Digit Span - Backwards; Spatial = Spatial Recognition Test (CANTAB); RPS = Rivermead Behavioural Memory Test - Profile Score.

PROBABILITY: *P<0.05, **P<0.01, ***P<0.001.

Factor analysing the Krawiecka symptom ratings and the neuropsychological tests which distinguished between the patient groups, identified five factors within eight iterations:

(1) a "reality distortion - neuropsychological differences" factor, explaining 33% of the variance, with hallucinations (-.37), delusions (-.45), and all cognitive tests (.46 to .88);

(2) a "psychomotor poverty" factor, explaining 15.5% of the variance, with flat affect (.77), poverty of speech (.80) and psychomotor retardation (.88), together with the RPS (-.34);

(3) an "affective factor", 10.9% of the variance, with depression (.80) and anxiety (.89);

(4) a "positive symptoms" factor, explaining 8.5% of the variance, including incoherent speech (.90) and the CPT-I error score (.57); and

(5) a final "disorganisation" factor, explaining 6.7% of the variance, of inappropriate affect (.73), with the MMSE (.42) and Verbal Fluency (-.44).

Table 2.10 (overleaf) shows Spearman-rank correlations between tracer uptake on SPET, normalised to occipital uptake, and MRI volumes, with these five factors. Only seven, relatively weak, correlations were found with SPET uptake, out of 140 comparisons. However, some consistent positive and strong correlations were found with MRI volumes: between Factor 1 and the left and right temporal lobes (i.e. larger temporal lobes, fewer positive symptoms and better cognitive function) and between Factor 2 and the volumes of the left and right lateral ventricles (i.e. larger ventricles, more negative symptoms and worse performance on the RPS).

Table 2.10 - Spearman rank correlations between the five factors, derived from symptom ratings and the distinguishing neuropsychological tests, and regional SPET tracer uptake (normalised to the occipital uptake and MRI regional volumes

	FACTOR 1	FACTOR 2	FACTOR 3	FACTOR 4	FACTOR 5
Left Anterior Cingulate (+4cm)	-.16	**-.35***	.01	.02	-.15
Left Anterior Cingulate (+6cm)	.01	-.05	.14	-.07	-.14
Left Caudate (+4cm)	.03	-.17	.15	.07	-.04
Left Frontal (+4cm)	.15	-.04	-.07	.04	-.21
Left Frontal (+6cm)	-.09	-.05	.01	-.05	-.06
Left Frontal (+8cm)	-.09	.03	-.05	-.19	-.13
Left Anterior Temporal (+4cm)	.09	-.33	.16	.20	-.10
Left Parietal (+6cm)	-.13	-.14	-.16	.17	-.23
Left Parietal (+8cm)	-.13	.16	-.18	-.07	-.09
Left Posterior Cingulate (+4cm)	-.21	.01	-.15	.18	-.04
Left Posterior Cingulate (+6cm)	.00	.10	-.26	.14	-.07
Left Putamen (+4cm)	-.01	-.25	-.21	-.15	-.08
Left Posterior Temporal (+4cm)	.12	-.22	.04	.19	-.10
Left Thalamus (+4cm)	.12	**-.38***	**.38***	.09	.08
Right Anterior Cingulate (+4cm)	-.17	**-.39***	-.14	.05	-.16
Right Anterior Cingulate (+6cm)	.04	-.01	.16	-.11	-.12
Right Caudate (+4cm)	.07	-.25	-.07	.17	.04
Right Frontal (+4cm)	.13	-.03	.04	-.09	.03
Right Frontal (+6cm)	-.01	-.18	**-.40***	-.21	-.01
Right Frontal (+8cm)	-.13	.14	-.06	-.30	.14
Right Anterior Temporal (+4cm)	-.03	**-.35***	-.11	-.13	.07
Right Parietal (+6cm)	-.04	-.33	-.20	-.22	-.18
Right Parietal (+8cm)	-.06	.16	-.27	-.27	.30
Right Posterior Cingulate (+4cm)	-.17	-.09	**-.35***	.17	.19
Right Posterior Cingulate (+6cm)	-.13	-.01	-.30	.20	-.25
Right Putamen (+4cm)	.04	-.30	-.14	-.08	.15
Right Superior Temporal (+4cm)	.24	-.29	-.05	-.02	.19
Right Thalamus (+4cm)	.09	-.19	-.04	.06	-.20
Whole Brain Volume	**.41***	-.05	-.13	.02	.25
Intracranial CSF	.17	.01	-.09	-.05	.05
Left Temporal Lobe	**.68*****	-.01	-.06	.11	.19
Right Temporal Lobe	**.55****	-.17	-.33	-.00	.11
Left Hippocampus	-.05	-.17	-.07	-.02	-.00
Right Hippocampus	-.07	-.22	.06	-.01	.10
Left Pre-Frontal Lobe	**.34***	.02	.08	.11	.08
Right Pre-Frontal Lobe	.24	-.18	-.06	-.17	.15
Left Lateral Ventricle	.15	**.40***	-.24	-.20	-.03
Right Lateral Ventricle	.10	**.49****	-.07	-.24	.00
Third & Fourth Ventricles	-.05	.25	-.22	-.31	.32

KEY: FACTOR 1 "Reality Distortion-Neuropsychological Differences"; FACTOR 2 "Psychomotor Poverty"; FACTOR 3 "Affective"; FACTOR 4 "Positive Symptoms"; FACTOR 5 "Disorganisation".
PROBABILITY: *P<0.05, **P<0.01, ***P<0.001.

2.4 DISCUSSION

The main finding of this study is that patients with treatment resistant schizophrenia do not have a statistically significant lower volume of brain structures on MRI or reduced tracer uptake on SPET as compared to treatment responsive patients. However, several differences were found between the groups on neuropsychological testing, and the RPS remained significant after controlling for several possible confounders. Possible reasons for the negative findings on the brain scans include: the patient groups were not sufficiently dichotomised, the study was not sufficiently powerful to detect statistically significant differences, the heterogeneity inherent in schizophrenia masks any differences between sub-types, and/or that such biological differences do not exist between such patient groups.

Firstly, it is clear from the available clinical information on the patient groups that they were markedly different in terms of their medication response, most symptom levels, measures of abnormal movements, social and global outcomes, and occupational levels. While practical considerations limited the dichotomy, the groups were certainly different by clinical comparisons and were sufficiently so as to detect differences in cognitive performance. The patient groups in this study differed markedly in terms of "positive symptoms" or indices of "reality distortion" (hallucinations and delusions), but less so in what have been labelled "disorganisation" symptoms (thought disorder, incongruity, irrelevance of speech), and hardly differed at all in the levels of "negative symptoms" or "psychomotor poverty" syndrome (Crow, 1980; Liddle *et al.*, 1992). These symptoms have been linked to pathological processes predominantly affecting neuronal networks in left-sided temporo-limbic structures, the right ventro-lateral pre-frontal cortex and the left dorso-lateral pre-frontal lobe respectively (Liddle *et al.*, 1992; Ebmeier *et al.*, 1993). Further, MRI studies have demonstrated reduced superior temporal gyral volume in hallucinating schizophrenics as compared to controls (Barta *et al.*, 1990; Shenton *et al.*, 1992). Although not significantly so, the volumes of temporal lobes and hippocampi were

substantially lower in the more severely hallucinating (treatment resistant) patients in this study, and these measures were fairly strongly correlated. The similarities between the patient groups on other symptom measures may account for the less marked group differences in the putatively important other brain areas.

Secondly, although there was no consistent relationship between SPET uptake and treatment response, it is noteworthy that almost all structures on MRI were smaller in resistant patients. This is compatible with a neurodevelopmental model of schizophrenia, where the more profound the cerebral aberration, the greater the effect on brain size, age at onset and clinical outcome (Weinberger, 1987). If this model is accurate the main problem in detecting subtle differences between patient groups is one of study power. For example, taking the best reproduced abnormalities between schizophrenics and controls, relative enlargement of the lateral ventricles, and assuming that the difference between outcome sub-groups of schizophrenic patients is as high as 30% (Johnstone *et al.*, 1989b) - as compared to approximately 10% in this study - the variability of this measure in schizophrenics is such that study groups of 100 members each would be necessary to detect a statistically significant difference (Gore & Altman, 1982). Similarly, considering the largest effect size (or standardised difference) between response groups in this study, that of 0.46 for right temporal lobe volume differences, two study groups of 80 members each would be needed for this to be statistically significant (Gore & Altman, 1982).

Thirdly, and more generally, outcome in schizophrenia can be influenced by a variety of factors which need not be directly illness related, such as the effects of medication and aspects of care, or other individual and external factors (May & Goldberg, 1978). Moreover, although the clinical course is usually established relatively early in the illness, some individuals may be misclassified and a sub-group of initially responsive patients may relapse within two years of maintenance treatment and remain refractory to further treatment thereafter (Kane & Lieberman, 1987). However, the patients in this study, although selected for differing treatment response, were different on all the

outcome measures employed, and there are no indications, thus far, that any of the 40 patients were misclassified. Such plentiful sources of confounding might obscure an association between MRI or SPET and treatment response, yet it could be argued that a substantial biologically or clinically important effect should be detectable above such 'noise'.

The results from CT studies examining the relationship between morphological abnormalities, usually lateral ventricular enlargement, and treatment response have been conflicting. In the studies directly addressing this question, two main approaches are discernible. Firstly, schizophrenic patients are selected for a particularly high VBR (usually two standard deviations above a control group mean) or not, prior to administering treatment; those with large ventricles generally (Weinberger *et al.*, 1980; Schulz *et al.*, 1983b; Luchins *et al.*, 1984), but not always (Nasrallah *et al.*, 1983a; Nimgaonkar *et al.*, 1988), respond less well to neuroleptics, in terms of symptomatic improvement. Alternatively, individual patients, assigned to relatively good or bad outcome on a *post hoc* basis, have had their symptom improvement scores correlated with VBR; an approach that has sometimes shown a strong negative correlation (Smith & Maser, 1983; Smith *et al.*, 1983; Kolakowska *et al.*, 1985; Pandurangi *et al.*, 1989; Schroder *et al.*, 1993), or no relationship (Williams *et al.*, 1985; Nimgaonkar *et al.*, 1988), but more often found a paradoxical association between a high VBR and a trend towards better neuroleptic response (Smith *et al.*, 1985; Boronow *et al.*, 1985; Losonczy *et al.*, 1986; Wilms *et al.*, 1992; Bersani *et al.*, 1995). The latter technique has also found a relationship between "delayed" neuroleptic response and third ventricle size in one study (Kaplan *et al.*, 1990), but not another (Boronow *et al.*, 1986), and no relationship with a number of global morphological measures (Smith *et al.*, 1987a). Clearly, there is no consistent linear relationship between ventricular enlargement and treatment response, at least on CT, as was confirmed in a recent meta-analysis of these studies (Friedman *et al.*, 1992).

A volumetric rather than area approach, using the relatively sensitive MRI rather than CT, on specifically selected patients, might better elucidate the relationship between neuroanatomy and outcome or treatment response. Certainly, previous MRI studies suggest an association between increased ventricular size and poor outcome (DeLisi *et al.*, 1992), or more negative symptoms (Young *et al.*, 1991; Gur *et al.*, 1994), and between reduced mesiotemporal volumes and more severe psychopathology (Bogerts *et al.*, 1993); similar to the correlations between Krawiecka scores and outcome measures with structure volumes in this study. However, very few other relevant MRI studies have been conducted. A group of outpatients have been dichotomised on a scale of deficit (negative) symptoms and studied with MRI (Buchanan *et al.*, 1993), but the patient group with more symptoms had larger volumes of all structures measured, approximating to those of a normal comparison group. Similarly, no cerebral volume differences were found between schizophrenics with favourable, intermediate or poor outcomes in another MRI study (Harvey *et al.*, 1993). These results support the findings of this study that there is no simple relationship between brain structure volumes and outcome or treatment response.

However, a tendency was found to an association between 'atrophy' and treatment response in the current study. Although this was only manifest in one of two analyses, both were planned comparisons. Previous studies of the relationship between treatment response and cerebral atrophy on CT have provided inconsistent results. Although treatment resistance has been related to general (Gattaz *et al.*, 1988) or frontal atrophy (Kaiya *et al.*, 1989; Friedman *et al.*, 1991) in some reports, others have found a curvilinear relationship with symptom improvement (Smith *et al.*, 1983) and the most frequent finding is of no significant association (Nasrallah *et al.*, 1983b; Boronow *et al.*, 1985; Smith *et al.*, 1987a; Nimgaonkar *et al.*, 1988, McCreadie *et al.*, 1989; Friedman *et al.*, 1992). Nonetheless, there are suggestions from the few relevant MRI studies of such a relationship. Jewart *et al.* (1991) found an excess of qualitatively abnormal scans in

patients who were resistant as opposed to responsive to clozapine, and Lieberman *et al.* (1992) reported a tendency to greater qualitative abnormalities in chronic multi-episode cases as compared to first episode subjects. One possible reconciliation of these discrepant findings is that cortical atrophy, or a loss of grey matter, represents a different disease process to the loss of white matter responsible for ventricular enlargement. This interpretation is supported by previous CT studies which failed to find a correlation between these measures (Weinberger *et al.*, 1989; Smith *et al.*, 1983; Boronow *et al.*, 1985), but in this and another MRI study (Lieberman *et al.*, 1992) a significant correlation - albeit weak - has been found. By contrast, no correlation was found in this study between atrophy and whole brain or CSF volumes. These quantitative measures are inevitably determined by the size of the head, which is highly variable, difficult to control for satisfactorily and subject to partial volume artefact. Qualitative ratings may automatically control for the former and is perhaps less subject to the latter. Thus, a standardised assessment of the degree of generalised loss of cerebral substance may be more sensitive to clinically relevant cortical atrophy than volumetric measurements of the whole brain. However, a further note of caution in the interpretation of this weak finding is that only one rater was used and there is therefore no guarantee of the reliability of this measure in the current study.

Previous SPET or PET studies of treatment response have also failed to identify definite associations with tracer uptake or receptor occupancy. There is only one comparable study to the current one, which employed PET. Buchsbaum *et al.* (1992) reported that a low metabolic rate in the caudate and putamen in 25 unmedicated patients predicted their subsequent response to haloperidol. Moreover, among responders, haloperidol 'normalised' striatal metabolism, while in non-responders it tended to exacerbate hypofrontality. The differences between these two studies could be attributable to the greater power of the Buchsbaum study - with a prospective within-subject design - or that they standardised the medication regimes of the patients during the

experiment. However, the rCBF values in responsive and resistant patients show no consistent pattern that would suggest a power problem in the present study and other functional imaging studies have established that poor clinical response to neuroleptics is not simply attributable to inadequate dopamine receptor blockade (Wolkin *et al.*, 1989; Coppens *et al.*, 1991; Pilowsky *et al.*, 1993).

The possibility remains that a sub-group of treatment resistant schizophrenic patients with marked structural brain changes could be delineated. This would be compatible with the great variability in MRI volumes within the patient groups in this study, which was more marked in the resistant group. In addition, the schizophrenic subjects with a particularly high number of HIS lesions tended to be those with a poor response in both this study and one other (Harvey *et al.*, 1993). As already discussed, previous CT studies of patients with ventricular:brain areas two standard deviations above a control mean have generally identified a group of patients with a poor treatment response (Weinberger *et al.*, 1980; Schulz *et al.*, 1983; Luchins *et al.*, 1984). However, these are findings in highly selected patient groups, and meta-analyses of the VBR in schizophrenia have failed to find any evidence for a bi-modal distribution (Raz & Raz, 1990; Daniel *et al.*, 1991b). This suggests that ventricular enlargement is not a marker for a specific sub-type of schizophrenia. Greater accuracy in predicting treatment response and outcome on an individual or group basis may be possible if additional factors are considered with brain structure, such as the many other biological variables that have been linked to treatment response (May & Goldberg, 1978; Lieberman & Sobel, 1993).

In this study, although imaging variables did not distinguish the patient groups, the cognitive testing did - particularly long-term episodic memory functioning (RPS). The relative selectivity of this finding argues against it being attributable to symptomatology, attention or co-operation; and it withstood controlling for intelligence or global functioning, pre-morbid education and medication levels. The RPS is determined over a comparatively lengthy and complex series of sub-tests (but no more so than, for example,

the delayed matching task) that were devised to measure aspects of memory in everyday use (Wilson *et al.*, 1985). Several previous studies have shown that schizophrenic subjects have cognitive deficits, primarily of memory, learning and concept formation, as compared to controls (Goldberg *et al.*, 1990; Saykin *et al.*, 1991; Frith *et al.*, 1991). Indeed, further evidence suggests that schizophrenics exhibit a relatively specific pattern of neuropsychological abnormality - primarily that of impaired long-term memory - akin to a dysmnesic syndrome (Tamlyn *et al.*, 1992; Goldberg *et al.*, 1993), and that these deficits are related to symptom and outcome measures (Goldberg *et al.*, 1990; Frith *et al.*, 1991). Although there are also reports of deficits in executive tasks (Shallice *et al.*, 1991), as in this study, the results replicate findings of particular deficits in memory, and suggest that these are strongly related to treatment response (and outcome). In general, cognitive deficits are associated with negative symptoms, ventricular enlargement and a poor outcome (Johnstone *et al.*, 1976 & 1978; Golden *et al.*, 1980 & 1982; Kemali *et al.*, 1985), and the few previous studies of treatment response tend to find stronger correlations with attention rather than memory (Smith *et al.*, 1992; Goldman *et al.*, 1993) but the RPS is a more sensitive test of memory functions that are important in the daily lives of patients. This is supported by the observation that the RPS correlated more strongly with clinical variables than the other, more traditional, cognitive tests.

The correlations between the RPS with both positive and negative symptoms, and with both the "reality distortion" and "psychomotor poverty" factors, is in keeping with previous findings (Goldberg *et al.*, 1990; Tamlyn *et al.*, 1992), and suggests that memory dysfunction is intrinsic to schizophrenia, rather than to any one aspect of it. While it is perhaps unsurprising that the distinguishing neuropsychology tests correlated with the differentiating clinical measures, the pattern of associations with the five clinical factors argues that different but related pathological processes are responsible for these relationships (c.f. Frith *et al.*, 1991; Liddle *et al.*, 1992). Further support for this assertion comes from the fact that the RPS correlated equally strongly with whole brain, pre-frontal

and temporal MRI volumes, suggesting that global processes are important determinants of memory function. Indeed, all the cognitive tests showed remarkably consistent correlations with pre-frontal, temporal and whole brain volumes; arguing against crude structural localisation of neuropsychological functioning. The few previous MRI-neuropsychology correlational studies in schizophrenia describe a similar picture; an association between cerebral area and performance on the Stroop test (Andreasen *et al.*, 1986), a relationship between memory dysfunction and reduced temporal lobe area (Michele *et al.*, 1992) or cerebral volume (Kareken *et al.*, 1995), and strong correlations between executive or memory tasks and pre-frontal areas (Seidman *et al.*, 1994). Thus, such neuropsychological deficits probably reflect generalised brain dysfunction, but this may be most pronounced in temporal regions and on memory tasks.

Here, as in previous studies, poor outcome and more severe symptomatology has been related to neuropsychological impairment, although almost all of the psychological tests which distinguished the patient groups were no longer significant after taking account of years of education. Thus, the neuropsychological abnormalities appear to reflect a process that begins relatively early in life and has effects before the advent of psychotic symptoms. As such, it could be argued that controlling for years of education is not justifiable when this may be affected by the early manifestations of the illness itself, particularly in those who develop it at a young age. However, given that performance on nearly all neuropsychological tests is related to general abilities and educational attainment, some attempt must be made to control for these factors. The fact that the RPS remained robust, although not unaffected, to controlling for several possible confounders indicates the central importance of memory in schizophrenia, and suggests that poor memory functioning may predict a poor prognosis. For example, memory impairment may adversely affect treatment compliance, or hinder abilities on several everyday tasks.

2.5 CONCLUSIONS

In conclusion, the ability of episodic memory testing to distinguish sub-groups of patients with schizophrenia may mean that memory functioning is an important determinant of outcome in the disease. If a specific association with treatment response is independently confirmed, this would imply a biological relationship and possibly one of pathophysiological importance. Quantifiable differences are therefore detectable between treatment responsive and resistant patient groups, but it does not seem possible to reliably differentiate them using neuroimaging techniques. Neuropsychological tests, perhaps in association with other clinical and biological measures, might be able to delineate prognostic and possibly even aetiological sub-types of schizophrenia. There may be a sub-type of schizophrenia that is associated with grossly abnormal cerebral morphology and a poor outcome, but the findings of this and other studies suggest that illness outcome - or even treatment response - is too diverse an issue, and confounded by too many variables, to be predicted by currently available imaging techniques. The variability in other illness factors in schizophrenia appears to be greater than that related to outcome or treatment response.

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CHAPTER 3

STUDY II

I^{123}-IOMAZENIL BINDING ON SINGLE PHOTON EMISSION TOMOGRAPHY IN SCHIZOPHRENIA

3.1 INTRODUCTION

Although differences in 99mTc-Exametazime uptake were not found between the two groups of patients with schizophrenia, the 40 SPET scans constituted a substantial resource for further study. Normal control subjects were not included in the MRI and SPET study of treatment response but a normal comparison group was available from the MRC Brain Metabolism Unit control bank who had been scanned with identical methods. Results were also available for a group of 20 unmedicated schizophrenic patients and a further 10 patients with other non-organic non-affective psychoses (i.e. schizoaffective, brief reactive, paranoid and not otherwise specified psychoses) who had also not received any oral neuroleptics for at least two weeks or depot for at least two months. It was therefore decided to investigate previous but conflicting findings regarding frontal tracer uptake or neuronal metabolism on functional imaging in schizophrenia. The large group of patients available made it possible to increase the power of any statistical comparisons, to examine the effects of medication in the 60 schizophrenic or schizophreniform patients, and to conduct a preliminary investigation of the diagnostic specificity of any abnormalities identified. Moreover, the high resolution SPET technique employed in all 70 patients allowed a particular focus on distinguishing tracer uptake in lateral as opposed to medial frontal cortex, as the lumping together of these regions is one potential reason for conflicting results from earlier studies. Twenty controls were therefore selected from the MRC bank, who were balanced for age and sex with the 70 patients. The SPET scans of all 90 subjects were examined on just two regions of interest (frontal and cingulate) on three slices (4, 6 and 8 cm above the OML) to limit the possibility of Type I error. Mean tracer uptake was examined relative to occipital uptake as this part of the brain is least affected by any ventricular enlargement. Hyperfrontality was identified in lateral frontal regions in all unmedicated patients as compared with controls, but reduced left cingulate (and mesial frontal cortex) uptake was a common finding in all patients with schizophrenia - regardless of medication status (Ebmeier *et al.*, 1995).

This investigation therefore dissociated medial and lateral prefrontal cortical tracer uptake in psychosis and schizophrenia. Very similar results have also been reported from two other research groups using FDG-PET (Tamminga *et al.*, 1992; Siegal *et al.*, 1993). Tamminga and colleagues examined 12 actively psychotic patients with schizophrenia, who had been unmedicated for at least one month, and found significantly reduced regional cerebral glucose metabolism in the anterior cingulate and hippocampus as compared to normal controls. Moreover, these reductions were common to both deficit and non-deficit patient subgroups, whereas neocortical hypometabolism was only found in the patients with deficit schizophrenia (Tamminga *et al.*, 1992). Siegal and co-workers reported their findings in 70 unmedicated patients and 30 controls, all of whom were male, who were scanned whilst performing a version of the Continuous Performance Test (CPT). Relative hypofrontality was found in the schizophrenia subjects, which was more marked in medial than lateral frontal regions and on the right rather than left side, and negatively correlated with both positive and negative symptom scores (Siegal *et al.*, 1993).

These studies consistently point to anterior cingulate deficits as characteristic of all patients with schizophrenia. They are in agreement with the few previous functional imaging research reports that have attempted to distinguish between frontal and cingulate metabolism, which have found reduced activity in anterior cingulate cortex (Andreason *et al.*, 1992; Lewis *et al.*, 1992; Kawasaki *et al.*, 1992) and increased metabolism in lateral prefrontal regions (Wiesel *et al.*, 1987a; Ebmeier *et al.*, 1993). Further support and a possible pathophysiological basis for these findings has come from neuropathological research.

In a series of experiments, Benes and co-workers at Harvard have described a number of relevant abnormalities in the post-mortem brains of patients with schizophrenia. A blind quantitative analysis confirmed previous uncontrolled findings of reduced neuronal density in prefrontal, anterior cingulate and motor cortices (Benes *et al.*, 1986). Neuronal

aggregates were smaller and separated by wider distances in cingulate regions, particularly in layer II (Benes & Bird, 1987); accompanied by increased numbers of long vertical axons in layers II and III (Benes *et al.*, 1987). These findings were shown to be attributable to a reduction in the numbers of small neurones (interneurones) in most layers of the prefrontal and cingulate cortices, but most marked in layer II of the cingulate cortex (Benes *et al.*, 1991). Pyramidal neurone numbers were not significantly different between patients and controls, other than an increase in layer V of the prefrontal cortex in schizophrenic patients (Benes *et al.*, 1991). Moreover, the differences found were not attributable to the effects of potential confounders such as age, postmortem interval, or duration of specimen fixation; and were also noted in patients who were neuroleptic naive. This body of work suggested that gaba-ergic interneurones (basket cells) were reduced in number in the pre-frontal and cingulate cortical regions and predicted that this would be accompanied by a compensatory up-regulation of GABA-A receptors. The hypothesis was confirmed in a receptor binding experiment, where a preferential increase in bicucilline-sensitive ^{3}H-muscimol binding was identified in the superficial layers of cingulate cortex in 6 patients as compared to 8 controls (Benes *et al.*, 1992). Similar results, also implicating gaba-ergic abnormalities in schizophrenic patients, have also been reported by a number of workers examining both frontal and temporal areas with similar techniques.

Kiuchi and colleagues described an increase in ^{3}H-flunitrazepam receptor binding in 13 patients with schizophrenia, localised to medial and orbito-frontal cortex, temporal cortex and putamen, but not to other cortical areas such as the hippocampus (Kiuchi *et al.*, 1989). In addition, pre-synaptic GABA re-uptake sites have been shown to be reduced in left temporal areas by two research groups (Simpson *et al.*, 1989; Reynolds *et al.*, 1990). These neuropathological studies suggest that gaba-ergic abnormalities may be found in patients with schizophrenia. Modern *in vivo* imaging techniques do not suffer from artefacts related to retrospective design, cause of death (agonal) or post-mortem

related changes in the brain. It was therefore decided to conduct a neuro-imaging investigation of gaba-ergic functioning using the specific benzodiazepine receptor ligand I^{123}-Iomazenil (ethyl 7-iodo-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5a][1,4]-benzo-diazepine-3-carboxylate). Iomazenil can be used with SPET (Schubinger *et al.*, 1991), labels the same site as the more established PET ligand Flumazenil but with ten-fold higher affinity (Johnson *et al.*, 1990), and together with its longer *in situ* availability may therefore be superior to Flumazenil as an in vivo imaging agent (Woods *et al.*, 1991). A sub-group of the patients from Study I who had already been SPET scanned with Exametazime were selected to test the hypotheses that patients with schizophrenia would have increased Iomazenil binding in frontal and cingulate regions as compared to normal controls, and that low Exametazime tracer uptake would be associated with a relatively high Iomazenil binding in within patient comparisons.

3.2 METHODS

3.2.1. Subjects

Ten patients with DSM-III-R schizophrenia were selected - an equal number having had relatively high or low anterior cingulate Exametazime binding. Their mean duration of illness was 13.9 years (s.d. 10.3), with a mean current antipsychotic dosage of 380.5 chlorpromazine equivalents (s.d. 483.7). Patients were excluded if they were currently receiving benzodiazepine medication, and none of the subjects received any such treatment for two weeks before the scan. Ten controls were also recruited. There were 6 men and 4 women in each group, but the mean age of patients (36.7, s.d. 9.7) was substantially higher than that of the normal subjects (mean 26.1, s.d. 7.4).

3.2.2. Scanning procedure

The ten patients, and one of the controls, were studied with the Neuro-900 high resolution multi-detector NeuroSPECT (Strichman Medical Equipment Inc., USA) system located in the MRC Brain Metabolism Unit at the Royal Edinburgh Hospital. This imager has 572-hole collimators, which give an in-slice resolution of 7.5mm (full width at half maximum); the sensitivity of the instrument has been measured at 520 counts per second in a head sized phantom filled with 1 kBq of 99mTc per ml (Ebmeier *et al.*, 1991). Images were reconstructed in middle resolution mode with two iterations using dedicated software (Strichman Medical Equipment Inc. version 2.86b, 1993).

The remaining nine controls were examined with an identical scanner and reconstruction protocol at the Department of Nuclear Medicine, University of Amsterdam. However, 800-hole collimators were used, which give a spatial resolution of 6mm and a sensitivity of 315-520 counts per second with a phantom filled with 1 kBq of 99mTc per ml (Verhoeff *et al.*, 1993).

Prophylactic thyroid blocking was carried out with potassium iodide or iodate respectively. Subjects were scanned at rest, lying on the imaging table, with eyes patched

and background noise minimised. SPET scan studies were conducted using mean intravenous I^{123}-Iomazenil at doses of 161.5 MBq (s.d. 13.0) in patients and 120.8 MBq (s.d. 27.0) in controls.

3.2.3 Image and Statistical analysis

Mid-ventricular slices containing the basal ganglia, parallel to the OML plane (approximately +4cm.), were successively acquired between the time of injection and 250 minutes later. Data were available up to 185.4 (s.d. 7.4) minutes in patients and up to 153.0 (s.d. 50.0) in controls; and were taken from 73.3 (s.d. 2.2) minutes post-injection (i.e. after peak values) in the patients, and from 80.8 (s.d. 16.6) minutes in the controls. In patients, an average of 8.6 (s.d. 1.3) slices could be used; in controls an average of 10.1 (s.d. 5.3) slices.

Templates originally drawn from a neuroanatomical atlas (Talairach *et al.*, 1988) were fitted to the trans-axial slice by aligning the outer border of the template with the outer border of the cortex, which was determined visually as the 20% isocontour line of the activity map. The inter-rater error for cortical count densities is, in most cases, less than 5% (Ebmeier *et al.*, 1991; Verhoeff *et al.*, 1993). The template contained ten regions of interest on both sides (shown with results).

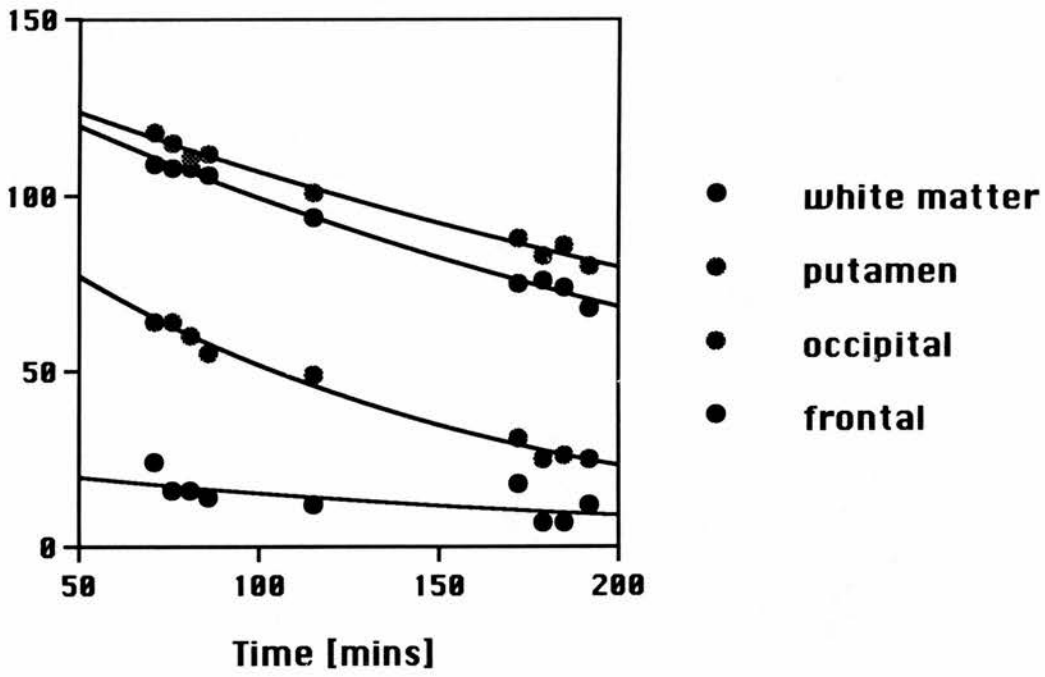
Two estimates of specific receptor binding capacity were derived from the non-linear (single exponential) regression of regional activity over time. Only estimates of regressions accounting for more than 50% of the variable variance were used. If the variance explained was less than 50%, this was attributable to increased noise rather than to a better fit of other non-linear models. The first measure was the regional elimination half-life computed from regional washout curves after 70 minutes (i.e. after regional peak measures), which has been shown to share a substantial amount of variance with estimates of specific binding capacity (Wood *et al.*, 1992). Secondly, regional Iomazenil uptake, extrapolated to the time of injection from measures after 70 minutes, was taken to

represent early delivery by regional perfusion and specific binding, as regional perfusion is known to affect the cerebral distribution of Iomazenil mainly at the early stages (Al-Tikriti *et al.*, 1994; Verhoeff *et al.*, 1993). In order to remove between-subject variability, extrapolated Iomazenil activity and half-lives were standardised to occipital regions of interest. Figure 3.1 (overleaf) shows the Iomazenil binding in selected regions of interest over the time of the experiment.

All ten patients had also been examined with 99mTc-Exametazime perfusion SPET an average of 16.9 months (s.d. 5.2) before the Iomazenil scan. These scans were acquired with a very similar protocol to the one used for Iomazenil (with injection at rest, eyes patched, and minimal background noise), and were re-analysed with the templates for this study to make the two imaging modes comparable.

Differences in receptor binding capacity, as measured by elimination half-lives, between the patients and controls were examined with Mann-Whitney U-tests corrected for multiple comparisons. Effect sizes for these comparisons were computed to predict the approximate group sizes required to demonstrate any such effects at statistically significant levels. Occipital uptake ratios of perfusion, receptor ligand binding and standardised elimination half-lives were compared within-patients with non-parametric statistical tests - using Friedman-Analysis of Variance followed by the Wilcoxon Matched-Pairs Signed-Rank Test. Estimates of specific receptor binding capacity were then correlated with perfusion measures from the Exametazime scans, using the Spearman Rank method, to determine the contribution of cerebral blood flow patterns to Iomazenil binding. This was done for both individual regional measures and across regions using group averages.

Figure 3.1 - Iomazenil regional washout curves over time



3.3 RESULTS

3.3.1 Iomazenil binding in patients and controls

The regional elimination half-lives of Iomazenil, in patients with schizophrenia and controls, are shown in Figures 3.2 and 3.3 (overleaf) and the values given in Tables 3.1 and 3.2 (on subsequent pages), on the left and right sides respectively. The values are within the range of previously published results (Woods *et al.*, 1992). On the left, Iomazenil binding was significantly increased in the patients in only the posterior cingulate region of interest ($P=0.01$), which was not in the predicted region and did not meet the level of significance required after Bonferroni correction ($P<0.0025$). Similarly, on the right side, the activity in the caudate was significantly elevated ($P=0.03$) and showed a tendency to be so in the posterior cingulate ($P=0.09$) but not to the extent required with control for multiple comparisons. In each of these regions the average number of slices available per patient was less than ten, as the proportion of variance explained in the non-linear regression was less than 50% in the remainder - meaning that those values were rejected. Tables 3.1 and 3.2 also show the effect sizes for these group comparisons of uptake ratios and standardised wash-out half-lives. With 10 subjects in each group, an effect size of at least 1.2 standard deviation units would be required to have a power of 0.8 to detect a statistically significant difference in planned comparisons. This translates to an overlap of at most one-third in the frequency distributions of the subject groups, and would give a clinically meaningful separation (Cohen, 1988) - whereas the effect sizes in the left and right anterior cingulate cortex were 0.5 and 0.4 respectively.

Figure 3.2 - Regional elimination half-lives (in minutes) of Iomazenil (left side)

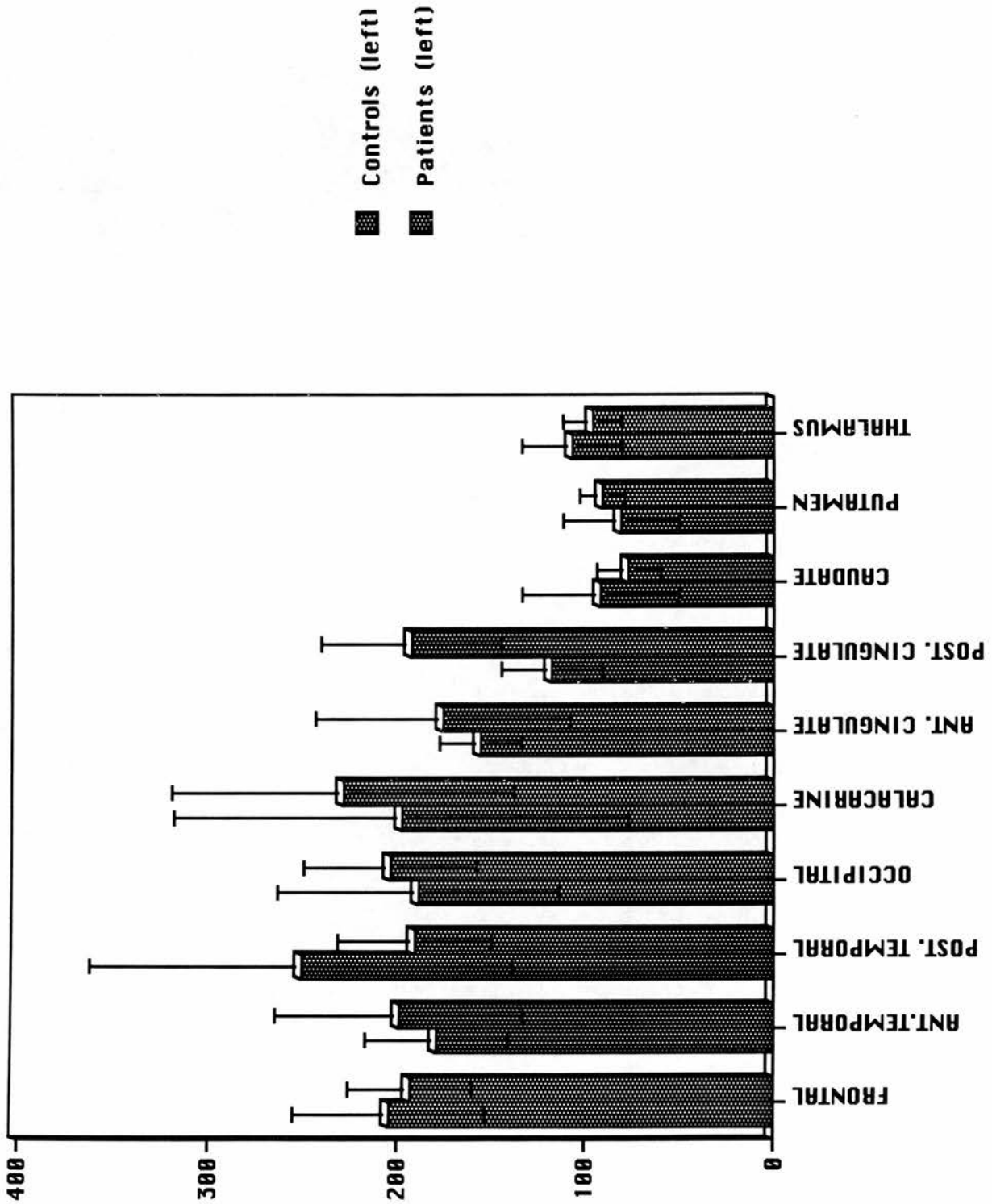


Figure 3.3 - Regional elimination half-lives (in minutes) of Iomazenil (right side)

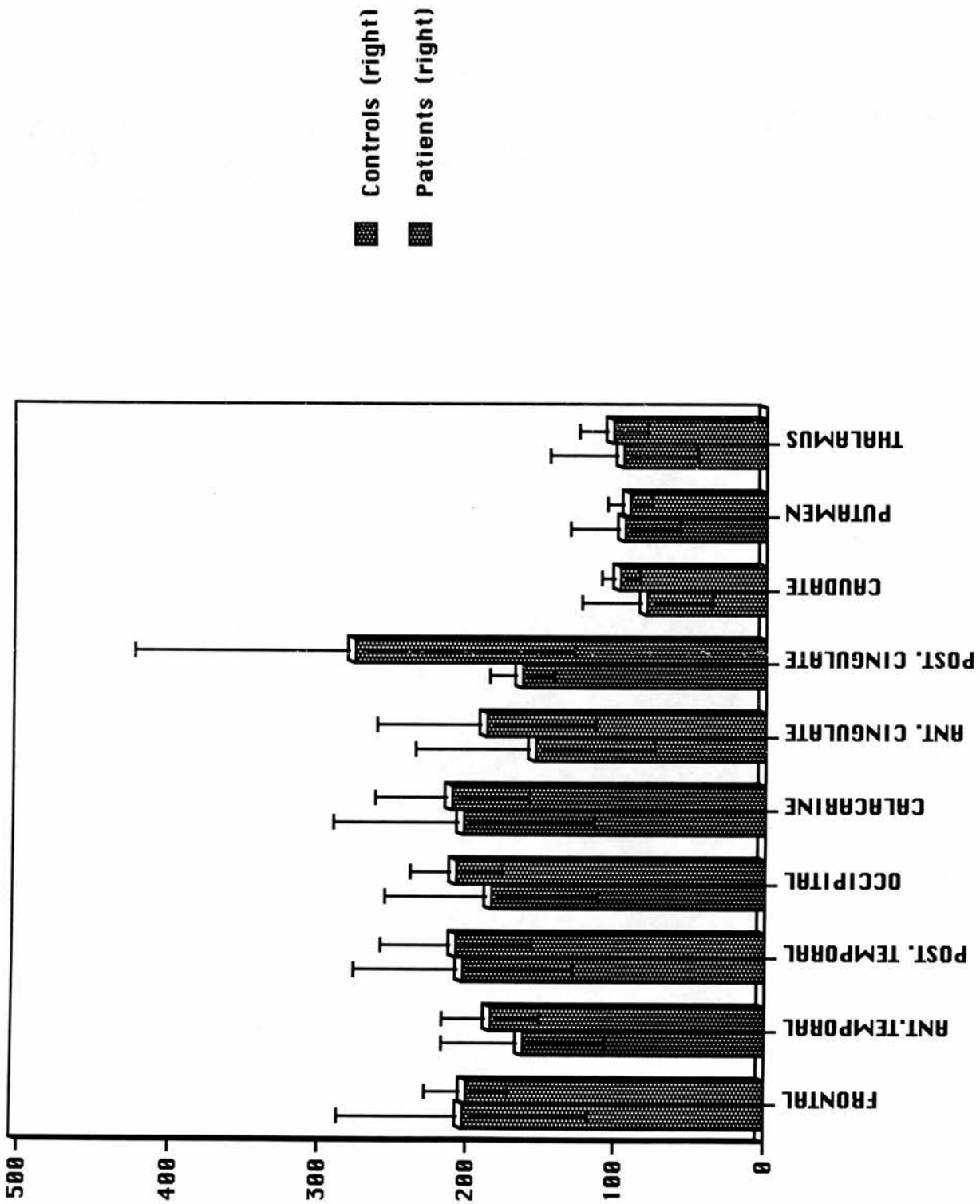


Table 3.1 - Regional elimination half-lives (mean, sd, N slices) of Iomazenil (left side)

	Controls		Patients		Effect sizes	P value*
	Mean (sd)	N	Mean (sd)	N	(Cohen's d)	(M-W U test
L FRONTAL	204 (51)	6	193 (33)	10	-0.2	-
L ANT. TEMP.	179 (38)	4	199 (66)	10	0.4	-
L POST. TEMP.	251 (112)	8	191 (41)	10	-0.8	-
L OCCIPITAL	189 (75)	8	204 (46)	10	0.2	-
L CALCARINE	198 (121)	6	229 (91)	10	0.3	-
L ANT. CING.	156 (22)	2	176 (68)	7	0.5	-
L POST. CING.	118 (27)	5	193 (48)	7	2.0	0.01*
L CAUDATE	92 (42)	6	77 (17)	10	-0.5	-
L PUTAMEN	81 (31)	7	91 (12)	10	0.5	-
L THALAMUS	107 (27)	6	96 (16)	10	-0.5	-

*significance level required after Bonferroni correction P<0.0025

Table 3.2 - Regional elimination half-lives (mean, sd, N slices) of Iomazenil (right)

	Controls		Patients		Effect sizes	P value*
	Mean (sd)	N	Mean (sd)	N	(Cohen's d)	(M-W U test
R FRONTAL	202 (85)	9	200 (28)	10	0.0	-
R ANT. TEMP.	162 (55)	8	184 (33)	10	0.5	-
R POST. TEMP.	203 (74)	9	208 (51)	10	0.1	-
R OCCIPITAL	184 (72)	8	208 (31)	10	0.5	-
R CALCARINE	203 (88)	5	211 (52)	10	0.1	-
R ANT. CING.	155 (81)	4	188 (74)	10	0.4	-
R POST. CING.	164 (22)	4	277 (148)	9	1.3	0.09
R CAUDATE	80 (44)	9	98 (13)	10	0.6	0.03
R PUTAMEN	95 (37)	8	92 (15)	10	-0.1	-
R THALAMUS	96 (50)	5	103 (23)	10	0.2	-

*significance level required after Bonferroni correction P<0.0025

3.3.2 Regional perfusion and Iomazenil binding in patients with schizophrenia

Tables 3.3 and 3.4 (overleaf) show the perfusion, extrapolated uptake and elimination half-lives on the left and right sides respectively in the ten patients with schizophrenia. In some of the small cingulate regions of *a priori* interest, values were excluded where the non-linear regression equation accounted for less than 50% of the overall variance. The only statistically significant differences between perfusion, uptake and elimination were in the left and right basal ganglia regions (see Tables). Although these differences were robust to controlling for multiple comparisons, the measures of receptor binding capacity were relatively lower than those of perfusion. In the only region of interest to show a tendency to the expected increase in binding (as measured with elimination half-life) - the right frontal cortex - the level of significance did not meet that required after Bonferroni correction ($P<0.003$).

These results are also shown in Figures 3.4 and 3.5 (on pages 144 and 145) to visually demonstrate the inter-relationships between the measures.

Table 3.3 - Occipital ratios of regional perfusion (rCBF), extrapolated uptake, and elimination half-lives in patients with schizophrenia (mean, sd, N of slices).

	rCBF	rUptake at t=0	rElimination t1/2	P (Friedman)*
	Mean (sd, N)	Mean (sd, N)	Mean (sd, N)	
L FRONTAL	0.86 (0.06, 10)	0.84 (0.07, 10)	0.93 (0.14, 10)	-
L ANT. TEMP.	0.93 (0.09, 10)	0.91 (0.13, 10)	0.94 (0.23, 10)	-
L POST. TEMP.	0.92 (0.08, 10)	0.90 (0.12, 10)	0.91 (0.15, 10)	-
L ANT. CING.	0.91 (0.13, 10)	0.90 (0.20, 7)	0.85 (0.42, 7)	-
L POST. CING.	0.84 (0.10, 10)	0.87 (0.15, 7)	1.01 (0.30, 7)	-
L CAUDATE	0.82 (0.10, 10)	0.62 (0.13, 10)	0.37 (0.09, 10)	0.0003
L PUTAMEN	0.98 (0.05, 10)	0.60 (0.12, 10)	0.44 (0.11, 10)	0.0002
L THALAMUS	0.94 (0.04, 10)	0.62 (0.09, 10)	0.46 (0.07, 10)	0.0002

*significance level required after Bonferroni correction P<0.003

Table 3.4 - Occipital ratios of regional perfusion (rCBF), extrapolated uptake, and elimination half-lives in patients with schizophrenia (mean, sd, N of slices).

	rCBF	rUptake at t=0	rElimination t1/2	P (Friedman)*
	Mean (sd, N)	Mean (sd, N)	Mean (sd, N)	
R FRONTAL	0.88 (0.06, 10)	0.83 (0.06, 10)	0.96 (0.11, 10)	0.06
R ANT. TEMP.	0.98 (0.06, 10)	0.97 (0.09, 10)	0.88 (0.13, 10)	-
R POST. TEMP.	0.94 (0.03, 10)	0.86 (0.08, 10)	0.99 (0.19, 10)	-
R ANT. CING.	0.95 (0.13, 10)	0.95 (0.16, 10)	0.88 (0.29, 10)	-
R POST. CING.	0.89 (0.09, 10)	0.89 (0.26, 9)	1.34 (0.67, 9)	-
R CAUDATE	0.88 (0.10, 10)	0.49 (0.10, 10)	0.49 (0.16, 10)	0.0004
R PUTAMEN	0.98 (0.05, 10)	0.62 (0.11, 10)	0.45 (0.12, 10)	0.0002
R THALAMUS	0.92 (0.05, 10)	0.61 (0.09, 10)	0.49 (0.08, 10)	0.0001

*significance level required after Bonferroni correction P<0.003

Figure 3.4 - Occipital ratios of regional perfusion (rCBF), extrapolated Iomazenil uptake (to time 0) and elimination half-lives in patients with schizophrenia.

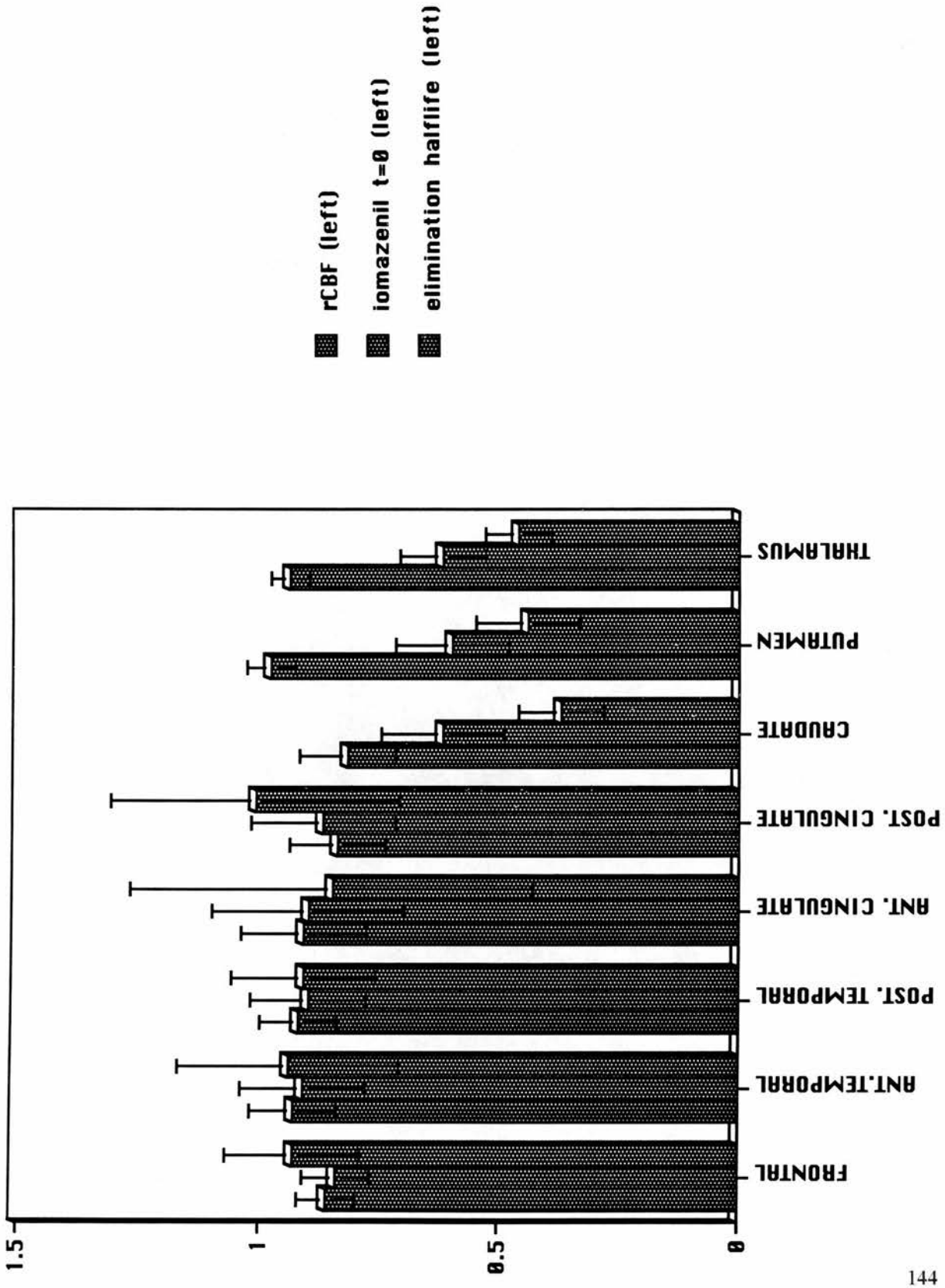
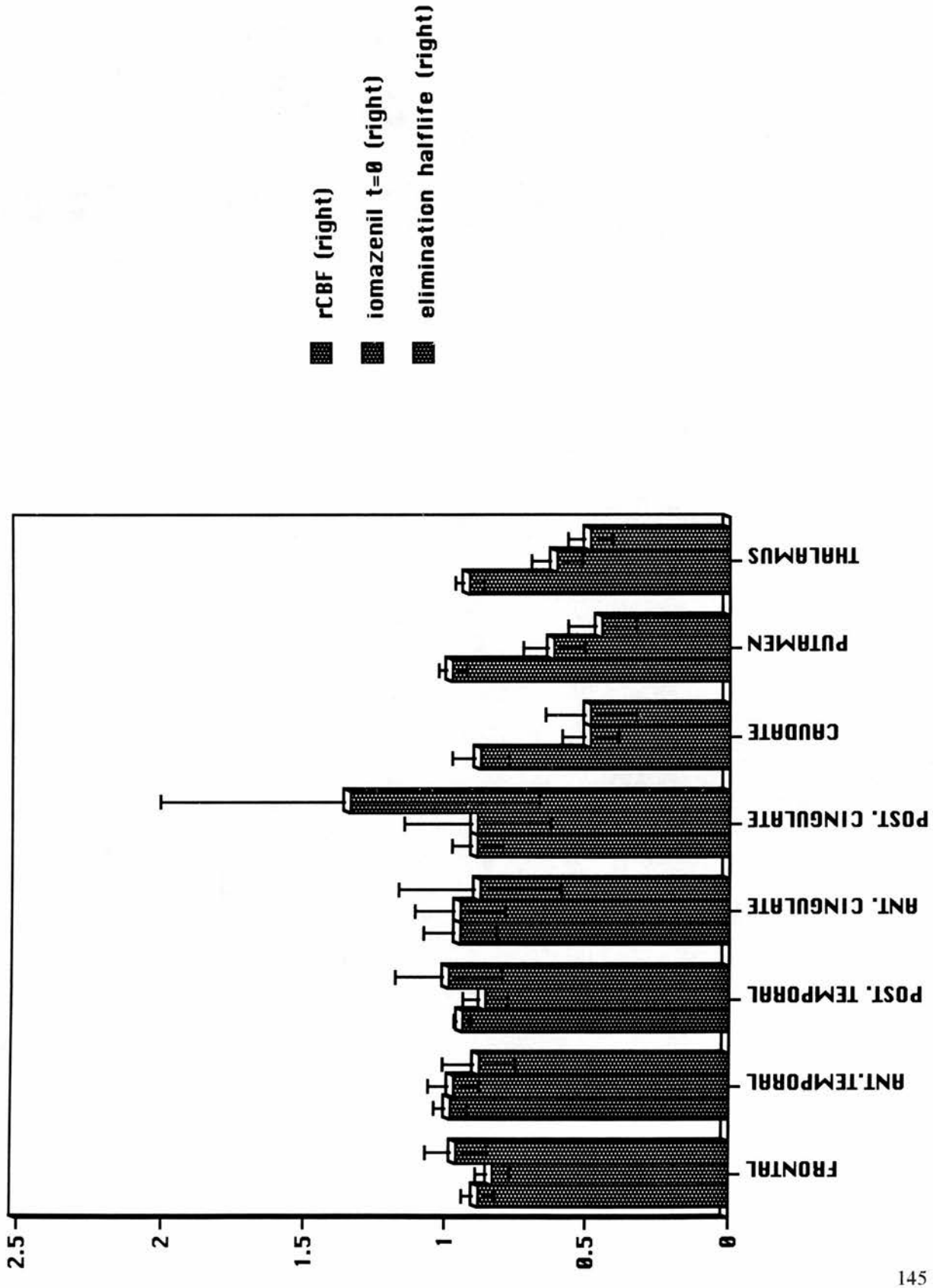


Figure 3.5 - Occipital ratios of regional perfusion (rCBF), extrapolated Iomazenil uptake (to time 0) and elimination half-lives in patients with schizophrenia.



3.3.3 Correlations between perfusion and extrapolated Iomazenil binding

As a final test of the hypothesis, Spearman rank correlation's were performed between Exametazime measured cerebral perfusion and Iomazenil receptor binding extrapolated to time zero. These are shown in Table 3.5 overleaf. Significant positive correlations indicate receptor binding potential commensurate with cell numbers and activity, absent correlations imply a lack of co-variance due measurement error or a change in perfusion between scans, and significant negative correlations suggest - as predicted - an inverse relationship between receptor binding and perfusion (i.e. a relative benzodiazepine receptor supersensitivity).

After Bonferroni correction for multiple comparisons, requiring a significance level of $P<0.003$, only one significant correlation in the left anterior temporal region ($r=.83$, $P=0.003$) and one trend in the left posterior temporal region ($r=.80$, $P=0.009$) remained. Between-subjects correlations in the other cortical regions also tended to be positive, but did not meet the required level of significance.

When group means were examined across regions of interest, cerebral perfusion was significantly and positively correlated with extrapolated receptor binding for the ten cortical areas ($r=.74$, $P=0.01$).

Table 3.5 - Spearman rank correlations between regional perfusion and extrapolated Iomazenil binding (normalised to the occipital cortex)

REGION	RHO	P VALUE*
Left Frontal	.50	0.1
Left Anterior Temporal	.83	0.003
Left Posterior Temporal	.77	0.009
Left Anterior Cingulate	.14	0.7
Left Posterior Cingulate	.54	0.2
Left Caudate	-.36	0.3
Left Putamen	.02	1.0
Left Thalamus	-.47	0.2
Right Frontal	.50	0.1
Right Anterior Temporal	.44	0.2
Right Posterior Temporal	.10	0.8
Right Anterior Cingulate	.38	0.3
Right Posterior Cingulate	.70	0.04
Right Caudate	-.25	0.5
Right Putamen	.58	0.08
Right Thalamus	-.10	0.78

* significance level required after Bonferroni correction $P<0.003$

3.4 DISCUSSION

In essence, the hypothesis of increased benzodiazepine receptor binding in the anterior cingulate and frontal cortex in schizophrenia suggested by the post-mortem literature was not confirmed. Although significant differences were found, in within patient comparisons, of regional elimination half-lives of Iomazenil as compared to Exametazime uptake in the basal ganglia, binding was significantly lower than perfusion estimates in these regions and the correlations between these measures were generally positive.

The potential explanations for the essentially negative results in the case-control experiment include the possibilities of Type II error due to inadequate power or methodological failings, or that the null hypothesis is correct and that the post-mortem studies have been subject to Type I error. Unfortunately, the design of the current study does not allow much certainty in accepting the null hypothesis. Using two groups of ten subjects each gave sufficient power to identify clinically significant effect sizes of at least 1.2 standard deviation units in 80 out of 100 planned comparisons (Cohen, 1988), and the estimated effect size from one anatomical study was of 2.0 (Benes *et al.*, 1992). The effect sizes for differences in the anterior cingulate identified here were only of the order of 0.5, which would demand approximately 60 subjects in each group to detect a statistically significant difference (Cohen, 1988). Thus, although the study was planned with sufficient numbers, based on the pre-existing literature, the relatively small effect observed could be attributable to differences between in vitro and in vivo approaches - for example, the potential confounding of anxiety or current medications in studying live subjects - or to some methodological problems in the present study that may have increased measurement variance or 'noise'.

An obvious methodological problem is the large difference in ages between the patients and controls. Even in the relatively young age groups examined, increasing age is associated with reductions in cerebral perfusion (Gur *et al.*, 1986) and receptor binding

capacity (Wong *et al.*, 1984). Thus, the patients' more advanced age may have led to a systematic underestimation of Iomazenil binding in comparison to the younger controls and Type II error; although, in the absence of specific information of the effects of age on Iomazenil binding, it might be expected that these age effects would be balanced by parallel decrements in cerebral perfusion. The patients are also more likely to have been treated with benzodiazepines in the past than the controls, although none were treated within two weeks of the scan and the effect of previous treatment is likely to be relatively small (Sybirska *et al.*, 1993). Neuroleptic drugs reduce GABA levels (Lichtshtein *et al.*, 1978) and would therefore have exaggerated any tendency to increased receptor sensitivity and binding. It might be argued that the patients were receiving their second scan and may have been less anxious about the procedure than the controls, but endogenous gaba-ergic compounds do not substantially modulate Iomazenil binding (Innis *et al.*, 1991).

More particularly, there are several differences between the scanning protocols in the patients and controls that could have materially affected the results obtained. This is largely attributable to the fact that the patients were scanned in one centre and most of the controls in another, which was attempted because Iomazenil is an expensive ligand with limited availability. The lesser resolution of the scanner used in the patients (in Edinburgh) will have led to greater partial volume effects and reduced the likelihood of finding increases in binding in relatively small regions like the anterior cingulate. Similarly, the slightly shorter average time to image acquisition in the patients could have reduced group differences, as the predicted receptor supersensitivity in regions with low perfusion would have become more noticeable with time, but this was controlled for by extrapolating back to binding at time zero. Alternatively, the higher average dose of ligand administered in the patients, would have tended to produce a positive rather than a negative result. Lastly, the large variance of almost all measures, particularly in the controls, would have reduced the chances of finding significant differences in receptor binding.

An assumption of the analysis is that activity after approximately 70 minutes mainly reflects specific receptor binding capacity. This if justified because displacement studies in primates showed that the non-specific binding of Iomazenil was only about 10% at 120-330 minutes after injection of the radiotracer (Innis *et al.*, 1991). Moreover, from between 20 and 60 minutes after injection of the ligand onwards, the regional distribution of Iomazenil remains constant (Innis *et al.*, 1991), and has been shown to be very similar to that of labelled Flumazenil in PET experiments (Verhoeff *et al.*, 1993).

A final methodological issue of concern is that all the methods of estimation were relative (to the occipital region), so that global differences in receptor binding capacity would not have been detected. In the absence of arterial measures of free parent ligand, a quantitative modelling procedure was not employed, so that conclusions about absolute receptor binding are not possible (Abi-Dargham *et al.*, 1994). Using a bolus injection method and examining subjects after the respective regional peak densities meant that no true equilibrium was established at the time of scanning, so that non-receptor related factors such as ligand delivery to the brain (regional perfusion) and rate of disappearance from plasma could have differentially affected group measures. However, experience with metabolic and cerebral blood flow imaging suggests that quantitative modelling may actually increase noise and make it more difficult to discover regional abnormalities (George *et al.*, 1991). The possibility remains that any group differences in the reference region could have confounded the result, particularly as Iomazenil uptake is greatest in occipital regions (Innis *et al.*, 1991; Woods *et al.*, 1992). Putatively greater structural tissue losses in frontal than occipital regions in schizophrenia (see Chapter 1) are relevant considerations here, but the work of Benes (1991) - on which this study is based - suggests that any such losses are limited in nature and extent. Further, and perhaps most importantly, two other Iomazenil-SPET studies in schizophrenia have also failed to find any evidence of gaba-ergic upregulation (Busatto *et al.*, 1995; Schroder *et al.*, 1995b).

All in all, although inconclusive, the results presented here do not support suggestions from the post-mortem studies of gaba-ergic abnormalities in frontal regions and raise issues of possible confounding in those experiments. In this regard, the finding of increased muscimol binding in pre-frontal cortex (Hanada *et al.*, 1987) has been attributed to differences in the numbers of patients and controls who suffered sudden deaths or prolonged terminal illnesses (Shapiro, 1993). Moreover, the report of increased flunitrazepam binding (Kiuchi *et al.*, 1989) has been contradicted by Squires et al. (1993) who found widespread reductions in that same measure. It should be noted that the Benes studies describing an apparent loss of inter-neurones have not been independently replicated, were conducted on small numbers of subjects and that the patients with schizophrenia had 'prominent affective disturbance' (Benes *et al.*, 1991). Akbarian et al. (1995) reported no significant cell loss in any layer of the pre-frontal cortex in the brains of ten chronic schizophrenics who had no affective disturbance, and there is even the possibility of an increased neuronal density in this area (Selemon *et al.*, 1995). Indeed, Squires et al. (1993) have suggested that the loss of small cells described by Benes and colleagues may have actually been attributable to deficits in the numbers of small pyramidal neurones, which could have been mistaken for basket cells. They went on to suggest that other interpretations of the increased binding of ^{3}H-muscimol (Benes *et al.*, 1992) are plausible - including a hyperinnervation by gaba-ergic neurones on larger pyramidal cells or an intrinsically larger number of high affinity GABA-A receptors in schizophrenia - which may better fit the findings from post-mortem neurochemistry studies and the results from the present study.

The reduction in Iomazenil binding as compared to Exametazime measured perfusion of the thalamus, caudate and putamen within the patients with schizophrenia must be treated cautiously for several reasons. It was not expected and should therefore be regarded as a *post hoc* result. Almost 18 months, on average, elapsed between the scans and a progressive reduction in perfusion and binding cannot be ruled out. Partial

volume effects, reducing measured perfusion/binding, are most marked in such small regions, especially those closer to the centre of the brain. Finally, Iomazenil uptake is lower and clearance higher in the thalamus and basal ganglia as compared to cortical regions (Beer *et al.*, 1990; Innis *et al.*, 1991; Woods *et al.*, 1992) and follows the known distribution of GABA receptors with least reliability in the thalamus (Beer *et al.*, 1990). Nonetheless, the size of the differences detected in the current study demands an examination of the relevant post-mortem studies.

The results are clearly compatible with those of reduced muscimol binding in the caudate (Hanada *et al.*, 1987) and reduced flunitrazepam binding in the globus pallidus (Squires *et al.*, 1993), but not with an increase of the latter in the putamen (Kiuchi *et al.*, 1989). At first sight, putative reductions in the numbers of GABA re-uptake sites in the putamen, caudate and lateral pallidum (Simpson *et al.*, 1992) would be expected to be associated with receptor supersensitivity, but similar findings in the left temporal cortex have not been shown to be accompanied by post-synaptic up-regulation (Simpson *et al.*, 1989; Reynolds *et al.*, 1990 & 1993). These findings, could conceivably be attributable to an excess of gaba-ergic transmission that may be localised to the basal ganglia (although a more generalised effect as suggested by Squires et al. (1993) would not be compatible with the results from the present study). Moreover, such an interpretation could be supported by functional neuro-imaging findings of a reduction in basal ganglia metabolism that is normalised by antipsychotic medication (see Chapter 1).

However, the status of any 'gaba-ergic hypothesis of schizophrenia', and particularly that of an increase in activity, has received at best inconsistent support from the literature. Early reports suggested that GABA levels were reduced in the nucleus accumbens and thalamus (Perry *et al.*, 1979) or amygdala (Spokes *et al.*, 1980), or only in the posterior hippocampus (Toru *et al.*, 1988). These have been challenged (Cross *et al.*, 1979), but there is no support for any increases in GABA concentrations. Similarly, CSF and plasma levels of GABA are generally normal, and have not been consistently related

to any particular illness characteristic (van Kammen & Gelernter, 1987). It could be claimed that the effects of antipsychotic drugs, in reducing GABA levels (Lichtshtein *et al.*, 1978), may account for these findings. However, if gaba-ergic activity in the brain were excessive, a parallel increase in the levels of the activity dependent Glutamic Acid Decarboxylase (GAD) would be expected, and while Hanada et al. (1987) described no such effect, Sherman et al. (1993) found a decrease, and a recent study has actually reported a reduction in GAD gene expression in the pre-frontal cortex (Akbarian *et al.*, 1995). These GAD activity results are the most consistent findings in this literature and are strong evidence against excessive gaba-ergic activity in patients with schizophrenia.

This literature review therefore strongly suggests that the findings of reduced Iomazenil binding in the thalamus and basal ganglia are methodological artefacts. Indeed, the only indisputable findings from the current study are of positive correlations between perfusion and receptor binding in left temporal cortex, which - given that structural abnormalities in schizophrenia are probably most marked in this region - is strong evidence that any benzodiazepine receptor deficits have little role in their aetiology. Some of the inconsistencies in previous studies could be attributable to regionally selective abnormalities in GABA levels and activity. Certainly, glutamatergic theories of schizophrenia, which are currently receiving intense interest, are based on similarly variable findings - although they do generally suggest an increase in activity in frontal regions and a reduction in temporal cortex and basal ganglia (e.g. Deakin *et al.*, 1989; Simpson *et al.*, 1992). Such findings have led to influential theories about glutamate function in schizophrenia (Carlson & Carlson, 1990; Olney & Farber, 1995), which have been modified to incorporate gaba-ergic components (Benes, 1993 & 1995) but it is difficult to advance a strong case that the latter are fundamental. Given that many neuropeptides are co-localised in neuronal populations, it is possible that many apparent deficits in gaba-ergic functioning are associated with and possibly attributable to glutamatergic abnormalities. Indeed, Squires et al. (1993) interpreted their findings of

reduced ^{3}H-flunitrazepam binding in the hippocampus as evidence of a loss of glutamatergic pyramidal cells because these normally outnumber gaba-ergic neurones in the cortex and would therefore be expected to have the greatest concentration of benzodiazepine binding sites. A putative disturbance in the afferent projections to the frontal cortex is suggested by glutamatergic hyperinnervation (Deakin *et al.*, 1989), and is also compatible with the original Harvard report of an increase in vertical axons in the cingulate (Benes *et al.*, 1986).

Finally, clinical observations and treatment trials do not support views that GABA activity is fundamentally disturbed in schizophrenia. Gaba-ergic drugs, such as baclofen, have occasionally been found to exacerbate psychotic symptoms, while benzodiazepines have at most small effects (van Kammen & Gelernter, 1987; Wolkowitz & Pickar, 1991). On the other hand, there are suggestions that excitatory amino-acids, such as glycine, may have a beneficial effect in negative symptoms at least (Javitt *et al.*, 1994), although replication is still required.

3.5 CONCLUSIONS

The main results from the present Iomazenil binding study do not support suggestions of an up-regulation in GABA receptors in the pre-frontal cortex of patients with schizophrenia. Rather, these findings and the inconsistencies in the previous literature go against the view that any disturbance of GABA functioning in schizophrenia is substantial or of primary importance. Unfortunately, the deficiencies of the present study demonstrate the many methodological factors that can confound neuro-imaging experiments and highlight the difficulties in conducting multi-centre research in this area.

Nonetheless, the combination of perfusion images with receptor binding scans is an exciting new experimental tool in brain imaging research, and one whose scope will increase with the development of other ligands of relevance to neuropsychiatric disorders. In vivo studies are complimentary to post-mortem experiments and do not suffer from artefacts related to agonal events and post-mortem or fixation intervals. If such technological advances are to be translated into important findings that will increase our knowledge of schizophrenia, researchers must carefully formulate hypotheses that can be tested in sufficiently large numbers of subjects to allow confidence in both positive and negative results. The following, final, chapter in this thesis will briefly discuss these issues.

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CHAPTER 4

THE FUTURE OF BRAIN IMAGING IN SCHIZOPHRENIA

4.1 INTRODUCTION

What developments in neuroimaging approaches to the study of schizophrenia and other neuropsychiatric disorders are likely in the foreseeable future? This question must be answered in terms of what is feasible as well as desirable, and cover likely advances in both technical and theoretical areas. These are important current issues for schizophrenia researchers as the initial enthusiasm accompanying new discoveries is gradually giving way to a more realistic appreciation of what has been achieved thus far. The neuroimaging findings have helped to demonstrate that schizophrenia is a disease of the brain, but have failed to consistently tie the pathognomic features of the illness to particular abnormalities. Without this, the deficits could be seen as nothing more than epiphenomena, especially as many workers have shown very similar abnormalities in a variety of other psychiatric disorders. This does not, of course, invalidate the findings but does pose very real questions about their specificity, and behoves researchers to harness the available technology to consistently demonstrate links between brain structure and function, as well as differences in these relationships between the major diagnostic groupings, symptom complexes and individual symptoms.

In these regards, technological developments promise to increase the sensitivity of the various measures of structure and function, but the simple application of such technical advances will not be sufficient to substantially increase knowledge about the pathophysiology of neuropsychiatric conditions. This will require new questions, framed as testable hypotheses, which can be addressed in such a way as to ensure confidence in both positive and negative answers. This chapter will briefly consider the likely technological advances, in both structural and functional neuro-imaging, over the next few years; before discussing desirable developments in theoretical and experimental approaches to the study of schizophrenia.

4.2 TECHNICAL DEVELOPMENTS

4.2.1 Structural imaging

Most MRI scanners now offer anatomical resolution as good as 1-2 mm. Further technical improvements are possible - which could reduce partial volume effects and other artefacts - but the main advances are likely to be in more reliable and automated volumetric assessments. Serial slice techniques, with internal anatomical boundaries, are prone to slice positioning artefacts, partial volume effects, parallax errors due to uncorrected rotation, and difficulties with naturally variable gyral boundaries. Surface rendering techniques can minimise these problems and provide more reliable volume estimations (Kulynych *et al.*, 1995 & 1996). Other methods to control for inter-subject variations in brain size and shape include linear transformation into a defined 'bounding box' (Andreasen *et al.*, 1994b), spatial normalisation to a template in stereotactic space (Collins *et al.*, 1994; Wright *et al.*, 1995) and landmark-based ('spline') deformations (DeQuardo *et al.*, 1996). Such methods may reduce measurement variability, which is usually most marked in patients, and might therefore be particularly useful when considering small differences between patient sub-populations and in cohorts over time. Automatic volumetric programmes, which substantially reduce image processing time, are already available for whole brain estimations, segmentation into grey and white matter and correcting tilt (e.g. Kohn *et al.*, 1991), but are unlikely to be able to discriminate particular lobes of gyri of interest.

The main technical advances in MRI are, in contrast, new developments in functional imaging techniques that are already rivalling PET and SPET, and may soon prove to surpass them, in terms of resolution, availability and safety.

4.2.2 Functional imaging

4.2.2.1 - PET and SPET

Future developments in PET, such as progressively smaller crystals and more powerful photomultiplier tubes for signal amplification, could substantially improve on the usual current spatial resolution of about 5mm - but basic positron physics limit the ultimate resolution to 2-3mm (Buchsbaum, 1987). Indeed, the need for an on-site cyclotron to manufacture radionuclides, and the ensuing expense and limited availability of the technique, mean that PET may have a relatively limited future as a neuroimaging method. Its main current advantage, of a wide range of radiopharmaceuticals with good biochemical sensitivity, will allow perhaps 5-10 more years of profitable experimentation - particularly in mapping the localisation of increasing refined neuropsychological tasks (after Petersen *et al.*, 1988) and in behavioural pharmacology of cognitive activations (e.g. Dolan *et al.*, 1995) - but advances in SPET and particularly functional MRI are likely to eventually make PET an expensive and unnecessary research tool.

Recent developments in SPET imaging include software improvements to allow sequential acquisitions (to discard movement degraded images), multiple angle imaging, dynamic filtering, surface variable attenuation correction and three dimensional display. Such instrumentation has brought SPET to the stage of rivalling PET for resolution and sensitivity. Workers in Edinburgh have now successfully adapted SPM for SPET, which will allow whole brain coverage and analysis of 'functional connectivity' (see below). New receptor ligands and a possible glucose analogue are being developed, which will allow relevant studies in large subject groups as a result of the relative inexpensiveness of SPET. In particular, improvements in energy resolution hold the promise of Dual Isotope Imaging, where 140 keV (^{99m}Tc) emissions could be distinguished from tracers of 159 keV (I^{123}) and absolute rCBF could be measured at the same time as ligand binding or rCBV (Devous, 1995). However, even SPET is unlikely to be able to compete with the major advantages of functional MRI.

4.2.2.2 Functional MRI

MRI hardware has already been adapted for functional studies of biochemical metabolism in Magnetic Resonance Spectroscopy (MRS), which can measure the concentration of metabolites as long as they contain paramagnetic nuclei such as phosphorus-31 (in ADP, ATP and phospho-esters), hydrogen-1 (in aspartate) and carbon-13 (in choline and fat). Although MRS studies in schizophrenia have suffered from poor resolution until very recently, there is some emerging consensus of reduced phosphomonoesters and inorganic phosphate in frontal cortex (Deicken *et al.*, 1994; Stanley *et al.*, 1995) and of reduced N-acetyl aspartate in temporal structures (Renshaw *et al.*, 1995; Maier *et al.*, 1995), which may reflect increased breakdown of neuronal membranes in schizophrenia. These studies promise to be able to examine similar measures of neuronal functioning as post-mortem receptor binding experiments, but without the confounding effects of old age and cause of death.

Another technique, still in infancy, is that of functional MRI (fMRI) which promises to revolutionise functional neuro-imaging. It measures activation increases in rCBF through a reduction in paramagnetic blood deoxyhaemoglobin content, without the need for radioactive contrast agents, and can therefore be employed in multiple scans over time with easy co-registration with structural MRI. Experience thus far in schizophrenia research is very limited, but preliminary studies have shown that such experiments can be done and have already highlighted reduced and less lateralised motor activations (Wenz *et al.*, 1995), a greater response to photic stimulation (Renshaw *et al.*, 1994), and reduced left frontal but increased left temporal activation during a word fluency task (Yurgelun-Todd *et al.*, 1996). Both MRS and fMRI are best conducted with larger field strength magnets, allowing fast imaging and improved resolution, but reliable results can be obtained with the more widely available clinical scanners. They offer spatial resolution in the millimetre range, and the concomitant use of electrophysiological techniques in 'multi-modal' imaging could provide complementary temporal resolution.

4.2.2.3 Electrophysiology

The main techniques used to date are those of Electoencephalography (EEG), Event Related Potentials (ERP's), and Brain Electrical Activity Mapping (BEAM); while recent technical developments include Magneto-encephalography and Transcranial Magnetic Stimulation (TMS). Their main advantage is of high temporal resolution, in the millisecond range, which is substantially greater than any currently available alternative techniques, and the lack of any exposure to radioactivity or X-rays. Their main problem, however, is the poor spatial resolution they offer, which may account for the somewhat inconsistent results obtained to date and their apparent lack of specificity (see Blackwood *et al.*, 1994). In general, brain activity recordings are made from overlying scalp electrodes and are therefore an indirect measure which can be affected by conduction through brain tissue and bone and movement artefact, particularly from eye muscles. For quantitative analysis, electrode placement has to be corrected for skull size, and signals have to averaged over many trials to be detectable above background noise. Nonetheless, some of these techniques are widely available and relatively cheap, so that more typical clinical populations can be examined outside the major centres.

The temporal information they provide about neural synchrony and network interactions bring interesting possibilities in correlating electrophysiology with other brain imaging techniques as composite measures of the sites and timings of putative abnormalities. For example, ERP amplitude reductions have been correlated with left temporal lobe measures and positive symptoms (McCarley *et al.*, 1993; Egan *et al.*, 1994), while latency may correlate with SPET tracer uptake in frontal and parietal cortex (Blackwood *et al.*, 1994).

It is apparent that functional and structural imaging methods are complementary and that their combined potential may substantially expand our knowledge of schizophrenia, but this will also depend on accompanying advances in our theoretical approaches to the disease.

4.3 THEORETICAL DEVELOPMENTS

4.3.1 Aetiological theories

What do we know about the cause(s) of schizophrenia, and what hypotheses does such knowledge generate that can be usefully tested in future studies?

Given that we can state with a fair degree of certainty that genetic factors account for 50-70% of the variance in liability to develop schizophrenia (McGuffin *et al.*, 1995), and that other risk factors such as obstetric complications (Geddes & Lawrie, 1995) and drug abuse (Andreasson et al., 1987) are well recognised, psychiatric researchers have relatively few theories of how these variables may interact pathophysiologically and lead to the development of the classical clinical picture. This is presumably related to the conceptual difficulty in formulating plausible links from aetiological factors, to biological abnormalities (of brain structure and function), to symptoms and signs. Three main 'grand' hypotheses have been advanced in recent years, two of which have been found wanting (Crow, 1980; Murray *et al.*, 1985) and the third has yet to be bettered, possibly due to its lack of specific predictions (Weinberger, 1987; Murray & Lewis, 1987).

Other theories have been proposed, concentrating on neurochemical disturbances such as in dopaminergic neurotransmission (e.g. Davis *et al.*, 1991) or localised structural deficits in the left hemisphere (McCarley et al., 1993) or the heteromodal association cortex (Schlaepfer *et al.*, 1994), but these have been limited in scope rather than attempting to link known abnormalities at other levels. Those models that have incorporated findings in several research fields are essentially modifications of the neurodevelopmental schema (e.g. Stevens, 1992; Keshavan *et al.*, 1994).

Crow's suggestion of two separate disease processes, mediated largely by dopaminergic overactivity and brain damage respectively (1980), has suffered the same fate as attempting to draw a distinction between familial and sporadic associations of aetiological factors (Murray *et al.*, 1985) - in research as well as clinical samples, these processes and factors do not conveniently dissociate from one another. It appears, rather,

that all are widely distributed amongst the patient population. The neurodevelopmental hypothesis, on the other hand, accommodates all these variables as predictive of schizophrenia - once triggered by biological and psychological events around puberty - with only subtle manifestations of a fixed lesion up until that point (Weinberger, 1987; Murray & Lewis, 1987). This 'hypothesis' is therefore more accurately referred to as a 'model', synthesising the available facts rather than delivering concrete refutable predictions. For example, if the current consensus that the structural brain changes in schizophrenia do not progress was seriously challenged by well executed studies, this would be incorporated into the model rather than requiring an abandonment of the hypothesis.

However, it is not the case that this model is therefore scientifically useless, according to Popper's falsifiability criterion. As an explanatory scheme it has much to commend it, in a similar way to Darwin's evolutionary ideas and in stark contrast with Freud's psychoanalysis - because they are or are not, respectively, based on empirical observations. Moreover, it is possible to induce testable propositions from the neurodevelopmental model if one is more specific about the period of development that is referred to and the putative processes involved at that time. Such an scheme has been suggested by Lyon & Barr (1991), who proposed that first trimester effects will lead to small brains, second trimester events to ventricular enlargement, and third trimester or perinatal factors to hypoxia and multi-site abnormalities.

The neurodevelopmental model has, of course, been built largely upon the findings of the neuroimaging literature in schizophrenia. Ironically, then, the fact that similar abnormalities have been found in structural, functional, and receptor binding experiments on subjects with affective disorders (see Chapter 1) - that may differ only in degree - argues that this model may equally apply to other psychotic disorders. Indeed, a 'continuum of psychosis' is also suggested by the overlap in symptomatology, treatment response and outcome (Crow, 1990), and recent demonstrations that neurodevelopmental

aberrations may also be found in patients with affective disorders (Sands & Harrow, 1995; Vocisano *et al.*, 1996). This suggests that these variables - which presumably reflect underlying commonalties in disease processes, whether integral to psychosis *per se* or merely as markers of severity - should be regarded as widely distributed in psychotic (and possibly all) populations for the purposes of both theorising and experimentation (see below).

This conceptual approach has been favoured by geneticists for some time (McGuffin *et al.*, 1995). Schizophrenia is regarded as the product of several genes (polygenic) that interact with each other and environmental factors (multifactorial) to increase or decrease the liability to the condition. It is important to recognise that apparent environmental effects, such as obstetric complications or drug abuse, may themselves be genetically mediated or the product of gene-environment interactions. Moreover, particular constellations of risk factors within individuals and over time could account for the co-existence of schizophrenia and affective psychoses within some families, the existence of schizo-affective psychoses, and individual diagnostic changes over time. Similar arguments, have been advanced for the relationship between anxiety and depression; where genetic factors may be essentially the same, but with phenotypic expression altered by environmental events (Kendler *et al.*, 1995). For example, certain genes may predispose to life events and the experience of 'stress' or maladaptive coping mechanisms (in anxiety or depression), and different genes to the substance abuse that can precipitate onset or relapse (in psychosis). An epidemiological, risk factor approach is necessary to provide empirical support or refutation of these possible interactions - as has been recognised for years in other multifactorial diseases e.g. ischaemic heart disease.

Unfortunately, very few studies have employed such an approach in studying schizophrenia, let alone psychosis more generally. Previously, researchers have tried to find neat but artificial distinctions between aetiological (Murray & Lewis, 1985) or pathophysiological factors (Crow, 1980), with little observable success. This is

unsurprising when one considers that 'abnormal' genes (and other risk factors) may be quite common in the general population (Harrison & Geddes, 1996). In the absence of a defined genetic abnormality, and a screening test for it, it is methodologically impossible to distinguish those at or not at genetic risk. (The family history is an unreliable proxy, and there may be different genes with differing effects within particular families.) Heterogeneity has been commonly invoked to explain such negative results, without distinguishing between genetic and phenotypic variance or testing the 'heterogeneity hypothesis' (see below). However, subtle refinements of these early theories, with explicit consideration of possible explanations of heterogeneity, have been recently proposed. For example, Lewis (1989) and particularly Castle & Murray (1991) have suggested a pathophysiological model that incorporates sex differences in onset and course of schizophrenia as well as a possible psychotic continuum. It remains to be seen whether such age at onset differences reflect different disease processes or are primarily manifestations of differing degrees of severity.

Other contemporary theories linking aetiological factors and pathophysiological processes are few and far between. Crow (1990) has again been one of the few to suggest a possible association between specific genetic and structural abnormalities; in postulating that anomalous cerebral asymmetry was of aetiological importance, as well as suggesting that a single 'asymmetry gene' was responsible for both brain development and psychosis. While the first part of this hypothesis has received some tentative empirical support, with demonstrations of a loss of asymmetry in schizophrenia and in those who apparently carry the gene (Bilder *et al.*, 1994; Honer *et al.*, 1995), it is extremely doubtful that only one gene is involved. Moreover, Crow's latest refinement of this theory - that links differential age at onset in the sexes to mating behaviour, and an equal worldwide prevalence to language and social intelligence and other species-specific behaviour (Crow, 1994) - is unlikely to find much scientific support given its vague nature, absence of logical steps and apparent lack of specific testable hypotheses. Indeed, it is difficult to see how any

language/social deficits that may be identified would favour his rather than the neurodevelopmental model. Although Crow's theory draws attention to our ignorance of the normal development of the human brain, it is all too easy to weave disparate threads of evidence into a model of some sort. This has been amusingly demonstrated by Birley (1993), who linked schizophrenia to other essentially human characteristics such as the phenomenon of sole heterosexuality, love, practising sex for pleasure and the disproportionately large size of the penis as compared to other primates. These speculative theories have the superficial attraction of apparently incorporating such important findings as the reduced emotional depth and sensitivity, decreased fertility and social deficits in schizophrenia - but, crucially, in an unfocused and untestable way. Small specific theories have greater scientific value than big vague ideas.

Neurochemical theories of schizophrenia, particularly the 'dopamine hypothesis', have substantial empirical support and potential links to genetic, structural and functional findings, but these have rarely been formulated in such a way as to be able to state that dopaminergic abnormalities are or are not associated with other specific biological disturbances (see Davis *et al.*, 1991). It has become clear that schizophrenia is not simply a hyperdopaminergic state and that a variety of other neurochemical abnormalities are likely to be involved. The best recent evidence of neuropharmacological disruption in schizophrenia has been realised from studies of glutamate receptors and a number of workers have proposed 'glutamate hypotheses' of the disorder (e.g. Carlsson & Olney, 1995). This accommodates known biological and clinical features of schizophrenia, such as structural changes and age at onset, as well as dopamine involvement. Moreover, it suggests some neurodegenerative component to the condition, through glutamate mediated excitotoxic neuronal damage, which challenges the simple neurodevelopmental conceptualisation of schizophrenia and is also compatible with observations that some cognitive impairments in schizophrenia show an apparent progression in the first five years of the illness (Bilder *et al.*, 1992). Excitotoxicity could account for poor prognosis in

many patients with schizophrenia, particularly those with the deficit syndrome, while its absence could explain the generally good outcome in affective disorders. This hypothesis has the advantage of a definite prediction - i.e. some degree of progressive volume reduction in some brain structures, particularly in the early stages of the illness

Psychological theories of schizophrenia have been largely discredited by the advances in our neuroscientific knowledge about schizophrenia. Latter day attributional explanations of psychotic phenomena (e.g. Roberts, 1992) are inherently mentalistic, but given our ignorance about mind-body relationships and the possibility that applications of such conceptualisation may have practical benefits for patients these should not be dismissed. The recent resurgence of interest in neuropsychology is of more immediate interest to neuroscientists conducting schizophrenia research as this has brought some definite conceptual advances, even though these have only rarely been tied to specific biological abnormalities. The new 'cognitive neuropsychology' is functionally oriented rather than lesion based, which is desirable given the latter's implications of specific cortical region involvement, but assumes that mental faculties are essentially modular - a proposition that may not be valid (see below). Nonetheless, genes may well code for cognitive processing tendencies - whether of modular capabilities or inferential propensities. Frith (1992) has perhaps made the greatest theoretical contributions in this area, in proposing abnormalities of 'self-monitoring' (leading to positive symptoms), 'self-generation' (negative symptoms), and 'suppression of inappropriate responses' (thought disorder and mood incongruence). These cognitive processes have also been neatly tied to particular patterns of regional brain metabolism (Liddle *et al.*, 1992), which might themselves be possible to trace back to structural brain changes. Although somewhat redolent of Kraepelin's three syndromes, which do not conveniently differentiate patient groups, they may represent different disease processes and provoke interesting questions - of general importance - as to whether such abnormalities reflect state or trait abnormalities and about their specificity and relationship with aetiological risk factors.

Frith (1992) has also borrowed the concept of abnormal 'theory of mind' from autism researchers to try and explain social deficits in schizophrenia. This has less intrinsic appeal, given the consensus that there are no substantive links between the two conditions and that social intelligence or cognition may be more accurate descriptions of the processes affected in schizophrenia researchers, but may ultimately prove of value if some association with underlying cerebral abnormalities (whether similar or different in schizophrenia and autism) can be found.

In summary, contemporary schizophrenia research seems to operate largely in a theoretical vacuum. Grand explanatory models are desirable in synthesising knowledge from disparate fields of research and in highlighting areas of potential interest, but must be accompanied by smaller, more specific and definite hypotheses. In many ways, a hypothesis that proves to be incorrect is as scientifically valuable than one which is right - we need more falsifiable theories rather than less. There is a need to link together known aetiological risk factors (genetic transmission, obstetric complications, drug abuse, and possibly schizotypy and social stressors), whether these act as predisposing or precipitating causes, with biological abnormalities (of brain structure and function) and thence to the cognitive deficits and characteristic clinical features of schizophrenia. It should be borne in mind that many of these aetiological variables are prevalent and widely distributed in the general and psychiatric populations. In many ways, however, our theorising about schizophrenia is constrained by our ignorance about how these agents may exert their pathophysiological effects and the possible interactions between them. Advances in our understanding of schizophrenia, therefore, will also be dependent on implementing new practical approaches to examining these possible effects. Given that we, broadly, know what causes schizophrenia, it should be possible to devise and conduct experiments that will further an integrated neuroscientific understanding of schizophrenia. A recent example of such an experimental approach is the series of studies conducted by Cannon *et al.* (e.g. 1989), which found that a large part of the variance in the propensity

to develop schizophrenia (in high risk individuals) was attributable to family history and obstetric complications, and demonstrated an interaction between levels of genetic risk and delivery complications with distinctive relations to ventriculomegaly and atrophy.

4.3.2 Experimental approaches

The main practical issue for schizophrenia researchers is how we can apply what we already know about the illness to realise further increases in our knowledge. It is clear that future studies will need to employ the best available epidemiological and neuroscientific techniques to answer important questions in such a way as to give confidence in the answers. The following pages briefly consider topical issues in epidemiological, psychopathological and neuroimaging approaches to schizophrenia; highlighting what studies are currently needed in each area.

4.3.2.1. Epidemiology

Epidemiology is narrowly defined as the study of the associations of disease in a population, but is also concerned with fundamental issues of study design and analysis. Much progress has been made in recent years in identifying risk factors for the development of schizophrenia (Cannon & Jones, 1996), and studies of gene-environment interactions are now required. Rutter has suggested that key questions include whether schizophrenia with neurodevelopmental precursors is any different from schizophrenia without them, and whether these factors primarily reflect genetic or environmental causes (Rutter, 1995). In seeking to answer these questions, researchers must consider the distribution of such risk factors in the general population as well as schizophrenic and other psychiatric patients.

Most research into schizophrenia is, understandably, conducted as case-control studies on clinical populations in large tertiary referral centres. The problem with this is that it is difficult to be certain that any abnormalities found are generalisable to all patients with schizophrenia or whether they are only representative of a sub-population. Patients in tertiary care are often the worst affected cases, raising the possibility that any findings are markers of severity rather than disease *per se*. Possible selection biases are difficult to overcome in small studies and the only reasonable alternatives are to conduct large

collaborative multi-centre studies or to identify cohorts of patients and controls from the general population. Multi-centre studies are laborious, expensive and do not bring prestige to individual researchers or departments; moreover, they may not be possible in high-tech areas such as neuro-imaging where different scanning protocols may confound results (as demonstrated in Study 2 of this thesis). Population based projects are probably therefore the best approach, with their advantage of generally representative patients and controls. Moreover, the large number of cases identified substantially increase statistical power.

Many neuro-imaging studies, as with much schizophrenia and medical research generally, are completed with relatively small numbers of subjects. Negative results (the null hypothesis) are therefore difficult to accept, given the likelihood of Type II error. Positive results, on the other hand, are generally accepted as they - with little if any consideration of possible Type I errors or confounding by case-control differences in small samples. Publication bias favours positive results and multiple significance testing ('data-dredging') for them. It is obvious that we need studies that are at least an order of magnitude larger than most previous research, with explicit prior hypotheses and multivariate statistical techniques to examine interactions and potential confounding, so that negative results can be accorded the same value as positive findings.

Negative findings are often attributed to 'heterogeneity', without further consideration of other possibilities or the nature of the apparent heterogeneity. Such assertions are of little scientific value, whereas it is possible to test for the existence of such variance and whether it is primarily genotypic or phenotypic (Carpenter *et al.*, 1993). For example, the extent of clinical differences within and between concordant monozygotic twin pairs identifies the source of such differences (Bailey *et al.*, 1996).
The use of these strategies, together with a generally greater awareness of epidemiological issues, are desirable goals for future research into the causes of schizophrenia.

4.3.2.2. Psychopathology

The difficulty in finding consistent clinical correlates of the biological abnormalities in schizophrenia has prompted experimental approaches designed to reduce heterogeneity. The most frequent method is to examine patients with and without a particular phenomenon of interest, which has been most widely used in the study of auditory hallucinations. These are, perhaps unsurprisingly, localised largely to language areas of the cortex (e.g. McGuire *et al.*, 1993 & 1995) in functional imaging experiments. However, localisation - regardless of accuracy - is not explanation: one could confidently predict that visual hallucinations reflect dysfunction in the occipital lobes without understanding why they occur. This approach does have value in seeking to link abnormalities of brain structure and function to cognitive and clinical findings (Mortimer & McKenna, 1994), but does not explain the characteristic form and content of auditory hallucinations in schizophrenia. Similar phenomena are also found in 10-15% of cases with severe affective disorders and the symptomatic approach may therefore tell us more about temporal lobe pathology generally than in any particular disease. Future studies should therefore focus on differences in form and content, within and between different disorders, and try to establish the modulation of these experiences as patients develop insight and the experiences become 'pseudohallucinations'. Functional MRI could be a valuable technique in the long-term follow-up studies required.

Similar elucidation is required of the possibly similar biological basis of negative symptoms in schizophrenia and depressive retardation (Dolan *et al.*, 1993). Studies of the objective behavioural concomitants of these problems may be illuminating; but it is clear that a purely symptomatic approach has limitations. This is likely to be particularly so where symptoms of illness are not qualitatively distinguishable from normal experience. For example, the remaining characteristic symptoms of schizophrenia - 'bizarre' delusions - clearly merge into partial delusions, which merge into overvalued ideas (such as anorexic 'fatness' and hypochondriacal disease conviction) and normal beliefs. Cultural

compatibility and the strength of conviction are the conventional discriminators, but these are arbitrary clinical judgements rather than objective differentials. Nonetheless, there is some potential in seeking to explain delusions as, for example, irregularities in access to and storage of particular memories (McKenna, 1991).

The symptom based approach necessarily precludes study of individuals without frank psychosis, whereas a number of schizophrenia related personality disorders aggregate in the families of affected individuals and may be risk factors for the condition. It will be important to examine how the childhood precursors and biological associations of schizophrenia relate to these forms of psychopathology. Clearly, a purely symptom based approach has some value but there is a need for sub-syndrome based (e.g. Liddle *et al.*, 1992) and disorder based research studies, with their differing but complementary capabilities.

4.3.2.3. Neuroimaging

Structural neuroimaging studies have provided valuable information about morphological abnormalities in schizophrenia, but has not as yet established the extent to which different parts of the brain are affected and how these changes relate to aetiological factors and clinical features. For example, do the loss of brain substance, ventriculomegaly, and asymmetry abnormalities reflect different disease processes related to particular genetic and environmental effects? This issue needs to be pursued in family and high risk studies, such as those by Cannon and colleagues (1989). In studying related individuals with and without psychosis, genetic heterogeneity related measurement variance is reduced and meaningful clinical correlations of biological abnormalities may be evident that would otherwise be obscured. Is the apparent reversal or loss or exaggeration of cerebral asymmetry meaningful or does it just reflect generalised reductions in brain volume? More studies need to examine these possibilities - with better control of tilt or rotation and blindness to side. To what extent are these structural changes purely trait

markers for the propensity to develop psychosis in the presence of other risk factors? By excluding schizophrenics with head injuries or those who are substance abusers, do we mis the opportunity to study the effects of these possible precipitants in those most likely to have brain changes?

Establishing reliable answers to these questions demands an epidemiological approach to both subject selection and data analysis i.e. large groups of population based patients and controls, with multiple regression analyses to control for confounders and co-variates (particularly head and whole brain size) and their interactions. The effects of medication, and a host of other possible confounders, cannot be adequately examined by simply ignoring them if they are not 'statistically significantly' different between study groups. These relationships need to be examined, as does the possibility of a degenerative component to schizophrenia, with knowledge of general population norms and it is only comparatively recently that some groups have started this endeavour (Gur *et al.*, 1991; Pfefferbaum *et al.*, 1994; Schlaepfer *et al.*, 1995; Murphy *et al.*, 1996). Perhaps most importantly, encouraging the use of standardised techniques between research centres will facilitate reliable comparisons between studies and allow the use of meta-analyses to examine larger numbers of subjects for weak but relevant associations.

Similar issues and questions are pertinent to the other main methods of brain imaging - functional mapping and neuropsychology - except these have the potential to discriminate state and trait abnormalities. However, conflating the two may account for some inconsistencies in the literature. Repeated studies over time, as possible with functional MRI, would clarify these effects and could examine for possible 'excitotoxic' decrements, but the test-retest reliabilities of functional imaging methods are largely unknown. More generally, we do not know enough about normal patterns of neuroreceptor binding patterns and metabolic profiles in different mental states. The physiological basis of the signals measured with various techniques requires further

elucidation: particularly as cerebral blood flow and metabolism are heavily influenced by levels of arousal and many psychoactive drugs (Mathew & Wilson, 1990 & 1991).

The physiological basis of activity related changes in regional cerebral perfusion or metabolism is also poorly understood. They two are assumed to be linear, but this assertion has limited empirical support at rest and some physiologic activations may actually uncouple perfusion and oxidative metabolism (Fox & Raichle, 1986); as could some pathological processes. Although much attention has been given to functional activations on cognitive tasks in normal subjects, particularly on PET (e.g. Petersen *et al.*, 1988), the standard 'subtraction method' may fail to reveal a region involved at both rest and activation, can sometimes indicate activation when there is no participation in a particular task and has difficulties interpreting reductions in metabolism (Horwitz & Sporns, 1994). Some of these problems may be attributable to variations in the resting state between subjects and have prompted greater interest in correlational data analysis strategies (Friston *et al.*, 1992a). Such analysis has the potential to examine the 'functional connectivity', or the temporal relationship between spatially remote neurophysiological events, of particular tasks. This explicitly acknowledges and measures activity in distributed neural networks, as probably underlies most cerebral activity, and is of considerable interest to neuroscientists generally.

A fundamental problem with the functional mapping of cognitive processes is the underlying assumption that such activity is essentially modular in nature. While this convenient, and therefore scientifically justifiable, it may not be valid. An obvious likely example of an exception to this rule is general intelligence (Anderson, 1990). This modular view of cognitive processing is partly a throwback to the original purposes of neuropsychology in lesion localisation, while the search for discrete impairments in schizophrenia has proved largely fruitless. As demonstrated in Study 1 of this thesis, conventional tests have limited ability to distinguish between sub-groups of schizophrenia whereas tests of more everyday functions may do so. It has been argued that the ability of

neuropsychological tests to identify abnormalities of brain structure and function or to act as specific cognitive probes has been exaggerated, while their utility in developing individually tailored treatments and in predicting outcome has been underestimated (Keefe, 1995). Apparently specific performance deficits could be attributable to not attending to the task or increasing task difficulty; while reductions in brain activation in patients and controls may simply reflect impaired concentration or the use of different strategies. Further progress in these areas is likely to require more use of paced cognitive testing and simple everyday measures of faculties such as memory and attention.

4.4 CONCLUSIONS

Twenty years of neuro-imaging research in schizophrenia has provided substantial gains in our knowledge and understanding of the disorder. Continuing technological developments have led to an increasing array of sensitive and complementary techniques to examine neuropsychiatric disorders, but these advances must be harnessed to test similarly evolving specific hypotheses in increasingly sophisticated experiments, rather than simply lead to explorative uses of new methods in old research paradigms.

Practically, a greater appreciation is required of the essentially normal distribution of most variables of interest to schizophrenia researchers. Each new generation of researchers applying the latest technological advances seem to have to re-discover that there are no neat dichotomies between schizophrenia and normal controls, let alone other disorders. This appears to be linked to the predominance of 'tertiary care' research rather than population based studies. We need more explicit theories, informed by a greater awareness of normal and abnormal brain development and degeneration, devised by those in a position to test them in large samples with multivariate statistical techniques.

A number of questions about schizophrenia stand out as both important and testable: the interactions between various risk factors at different time periods; any possible progression in biological abnormalities, particularly in the first five years of the illness; can distinct neurodevelopmental processes, rather than sub-types, be identified; and how specific are any such processes to schizophrenia, particularly as compared to other psychoses. Structural imaging experiments need to include more women in general, clarify issues about the size of the head and brain and possible asymmetry anomalies in schizophrenia, and examine the course of such abnormalities in long-term follow-up studies. Functional imaging, particularly fMRI, could establish if there are any identifiable traits predisposing to schizophrenia and, given that course may be the best discriminator between schizophrenia and affective psychoses, study changes over time. Neuropsychology studies would benefit from a greater use of measures of everyday

functioning, rather than tests derived from lesion studies, and trying to link deficits in them to the clinical characteristics of particular disorders. Recently proposed animal models of schizophrenia, of the effects of phencyclidene, could help to increase knowledge in each of these core areas. New strategies, such as examining the objective behaviour accompanying phenomena rather than just the symptoms themselves, may also be valuable. Older paradigms, largely overlooked in these days of 'biological psychiatry', such as the link between social stressors and relapse in schizophrenia, should not be forgotten.

With the combination of increasing sophisticated and sensitive neuro-imaging methods, novel theorising and rigorous hypothesis testing, within an integrated neuroscientific approach to neuropsychiatric disorders and brain-behaviour relationships (after Damasio, 1994), it is likely that substantial advances will be made in the near future in identifying the causes of schizophrenia.

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